```
=> d his

     (FILE 'HOME' ENTERED AT 15:36:49 ON 25 MAY 2000)
                SET COST OFF
                SET AUHELP OFF

     FILE 'HCAPLUS' ENTERED AT 15:36:59 ON 25 MAY 2000
                E CHUNG S/AU
L1           537 S E3-E27
                E CHUNG SHIH/AU
L2             6 S E4-E8
                E KENNEDY T/AU
L3            17 S E3,E14
                E KENNEDY THOM/AU
L4            30 S E4,E12,E13
L5             5 S E30
                E KNIGHT P/AU
L6            51 S E3,E9
L7            31 S E32,E39-E41
                E ROBINS D/AU
L8            14 S E3,E9-E11
                E ZEZHI J/AU
L9           384 S ZERANOL
L10        51814 S ESTRADIOL
L11         4013 S ESTRADIOL BENZOATE
L12          440 S TRENBOLON#
L13          275 S TRENBOLON# ACETATE
L14           45 S SOMATOTROPHIN#
L15         8530 S SOMATOTROPIN#
L16        40072 S TESTOSTERONE
L17         3947 S TESTOSTERONE PROPIONATE
L18         2951 S SALBUTAMOL#
L19        44247 S PROGESTERONE

     FILE 'REGISTRY' ENTERED AT 15:42:51 ON 25 MAY 2000
L20            1 S 26538-44-3
L21            1 S 50-28-2
L22            1 S 50-50-0
L23            1 S 10161-33-8
L24            1 S 10161-34-9
L25            1 S 9002-72-6
L26            1 S 58-22-0
L27            1 S 57-85-2
L28            1 S 18559-94-9
L29            1 S 57-83-0
L30           10 S L20-L29
                SEL RN
L31          356 S E1-E10/CRN

     FILE 'HCAPLUS' ENTERED AT 15:46:51 ON 25 MAY 2000
L32       108842 S L30
L33         1210 S L31
L34          727 S ZEARALANOL OR ZEARANOL OR MK188 OR MK 188 OR TRIENBOLON# OR R
L35       133969 S L9-L19,L32-L34
L36            7 S L1-L8 AND L35
                E SHIH C/AU
L37          344 S E3-E23
                E SHIH CHUNG/AU
L38           48 S E3-E10
                E SHAO Z/AU
L39           19 S E3
L40           22 S E16-E19
L41            3 S L37-L40 AND L35
L42            9 S L36,L41
L43            1 S L42 AND IMPLANT?
```

Point of Contact:
Jan Delaval
Librarian-Physical Sciences
CM1 1E01 Tel: 308-4498

1/1/99 filing date
If they want
11/4/98 they
need to claim it
on p. 1 of spec

Zeranol

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L44        29285 S LACTOSE
L45        17808 S MANNITOL
L46        18649 S SORBITOL
L47        88168 S SUCROSE
L48         7305 S DEXTROSE
L49        82582 S STARCH

     FILE 'REGISTRY' ENTERED AT 15:53:44 ON 25 MAY 2000
L50            1 S 63-42-3
                 E L-LACTOSE/CN
L51            1 S E3
                 E DL-LACTOSE/CN
                 E "(-)-LACTOSE"/CN
                 E "D-(-)-LACTOSE"/CN
                 E "L-(-)-LACTOSE"/CN
L52            1 S E3
                 E "L-(+)-LACTOSE"/CN
L53            1 S 69-65-8
                 E L-MANNITOL/CN
L54            1 S E3
                 E DL-MANNITOL/CN
L55            1 S 50-70-4
                 E L-GLUCITOL/CN
L56            1 S E3
                 E DL-GLUCITOL/CN
L57            1 S 57-50-1
                 E "(-)-SUCROSE"/CN
                 E "D-(-)-SUCROSE"/CN
                 E "L-(-)-SUCROSE"/CN
                 E "L-(+)-SUCROSE"/CN
L58            1 S 50-99-7
                 E L-GLUCOSE/CN
L59            1 S E3
                 E DL-GLUCOSE/CN
L60            1 S E3
L61            1 S 9005-25-8
L62           11 S L50-L61
                 SEL RN
L63            1 S E1-E11/CRN AND L31

     FILE 'HCAPLUS' ENTERED AT 15:57:29 ON 25 MAY 2000
L64         4117 S L62,L44-L49 AND L35

     FILE 'REGISTRY' ENTERED AT 15:58:32 ON 25 MAY 2000
L65            5 S 9004-57-3 OR 9004-67-5 OR 9004-62-0 OR 9004-65-3 OR 9004-32-4
L66           12 S 79-41-4/CRN AND 79-10-7/CRN AND 2/NC
L67            3 S L66 AND C4H6O2 AND C3H4O2
L68            2 S L67 NOT 57107-60-5

     FILE 'HCAPLUS' ENTERED AT 16:01:44 ON 25 MAY 2000
L69           76 S L65,L68 AND L64
L70          247 S L64 AND ?CELLULOS?
L71          138 S L64 AND ?ACRYL?
L72          355 S L69-L71

     FILE 'REGISTRY' ENTERED AT 16:02:24 ON 25 MAY 2000
L73           15 S 189943-94-0 OR 153439-97-5 OR 146447-66-7 OR 142227-56-3 OR 1

     FILE 'HCAPLUS' ENTERED AT 16:04:23 ON 25 MAY 2000
L74           14 S L73 AND L64
L75           55 S ?LACT?(L)?GLYCOL? AND L64
L76          396 S L72,L74,L75
L77           14 S L76 AND IMPLANT?
L78           14 S L76 AND ?IMPLANT?
L79           22 S L76 AND (COW OR CATTLE OR CALF OR VETERIN?)
L80            7 S L79 AND (1 OR 63)/SC,SX
```

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L81          19 S L43,L78,L80
L82          15 S L79 NOT L81
L83          26 S L76 AND ?INJECT?
L84           2 S L76 AND (IMMUNIZ? OR IMMUNIS?)
L85           1 S L84 AND (1 OR 63)/SC,SX
L86           9 S L83 AND (1 OR 63)/SC,SX
L87          25 S L81,L85,L86
L88          17 S L83 NOT L87
L89          20 S L76 AND (SHEEP OR LAMB OR PIG OR PIGLET OR SOW OR HORSE OR MA
L90          16 S L89 NOT L87
L91           1 S L90 AND 63/SC
L92           4 S L87 AND L89
L93          26 S L87,L91,L92
L94           4 S L76 AND SWINE
L95           3 S L94 AND 63/SC
L96          26 S L93,L95

=> fil hcaplus

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FILE COVERS 1967 - 25 May 2000  VOL 132 ISS 22
FILE LAST UPDATED: 24 May 2000  (20000524/ED)

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and title searches back to 1907.  The records from 1907-1966 now have
this searchable data in CAOLD.  You now have electronic access to all
of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.

=> d l96 bib abs hitstr tot


L96  ANSWER 1 OF 26  HCAPLUS  COPYRIGHT 2000 ACS
AN   2000:314511  HCAPLUS
TI   Improved growth stimulant compositions
IN   Shih, Chung; Kennedy, Thomas J.; Knight, Peter
     James; Robins, Daniel S.; Shao, Zezhi Jesse
PA   Schering Corporation, USA
SO   PCT Int. Appl., 24 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2000025743      A2   20000511       WO 1999-US23993  19991102
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ,
             DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP,
             KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO,
             NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
```

SO J. Biol. Chem. (1979), 254(17), 8270-5
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The effect of ethidium bromide (I) and actinomycin D (II) on the uterine nuclear estrogen receptor during the **estradiol**-3H exchange assay was studied. Uterine nuclear fractions were prepd. from ovariectomized rats that had received a 5-.mu.g s.c. **injection** of **estradiol** 1 h prior to killing. Incubation of nuclear fractions with **estradiol**-3H at 37.degree. resulted in a rapid labeling of nuclear estrogen receptor within 30 min which was followed by a loss of receptor sites that quant. resembled nuclear estrogen receptor processing. The addn. of I or II blocked this loss of nuclear estrogen receptor, resulting in a prolonged elevation of specific nuclear **estradiol** -3H binding. Examn. of the DNA by **polyacrylamide**-agarose gel electrophoresis showed extensive fragmentation that could be inhibited by II in a dose-dependent manner. These findings suggest that a nuclease(s) present in crude nuclear fractions was responsible for the DNA fragmentation and loss of nuclear estrogen receptor complexes. Nuclear estrogen receptor release and DNA hydrolysis did not occur in highly purified nuclei. Nuclear estrogen receptor lost at 37.degree. could be recovered in the supernatant fraction as a family of sol. macromol. complexes. Low salt **sucrose** gradients of this fraction showd specifically bound **estradiol**-3H in an aggregate fraction that sedimented to the bottom of the gradient, and a free 8 S form. Both of these were converted to a 6 S form in gradients contg. 0.4M KCl.

=> fil wpids

FILE 'WPIDS' ENTERED AT 16:48:23 ON 25 MAY 2000
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FILE LAST UPDATED: 24 MAY 2000 <20000524/UP>
>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK 200025 <200025/DW>
DERWENT WEEK FOR CHEMICAL CODING: 200025
DERWENT WEEK FOR POLYMER INDEXING: 200025
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE http://www.derwent.com/covcodes.html <<<

=> d his l97-

(FILE 'HCAPLUS' ENTERED AT 16:25:42 ON 25 MAY 2000)

FILE 'WPIDS' ENTERED AT 16:27:13 ON 25 MAY 2000
E US98-185944/AP,PRN
E WO99-US23993/AP,PRN
L97 3190 S L9-L19,L34
E ZERANOL/DCN
E E3+ALL/DCN
L98 23 S E2 OR 2051/DRN
E ESTRADIOL/DCN
E E3+ALL/DCN
L99 730 S E2 OR 0014/DRN
E ESTRADIOL BENZOATE/DCN

```
                E E3+ALL/DCN
L100         60 S E2 OR 0024/DRN
                E TRENBOLONE/DCN
                E E3+ALL/DCN
L101          8 S E2
                E TRENBOLONE ACETATE/DCN
                E E3+ALL/DCN
L102         10 S E2
                E SOMATOTROPIN/DCN
                E GROWTH HORMONE/DCN
                E TESTOSTERONE/DCN
                E E3+ALL/DCN
L103        446 S E2 OR 0156/DRN
                E TESTOSTERONE PROPIONATE/DCN
                E E3+ALL/DCN
L104         55 S E2 OR 0146/DRN
                E SALBUTAMOL/DCN
                E E3+ALL/DCN
L105        354 S E2 OR 2007/DRN
                E SALBUTAMOL/DCN
                E E4+ALL/DCN
L106         57 S E2
                E PROGESTERONE/DCN
                E E3+ALL/DCN
L107        618 S E2 OR 0145/DRN
L108       4074 S L97-L107
L109         17 S L108 AND (POLYLACTIDE OR POLYLACTIC OR LACTIDE OR LACTIC)()(P
L110        149 S L108 AND ?CELLULOS?
L111        260 SEA L108 AND (V71? OR V72?)/M0,M1,M2,M3,M4,M5,M6
                E POLYLACT/DCN
                E LACT/DCN
                E GLYCOL/DCN
                E POLYGLYCOL/DCN
                E CELLULOSE/DCN
                E ETHYL CELLULOSE/DCN
                E E3+ALL/DCN
L112       1193 S E2 OR 1858/DRN
                E METHYL CELLULOSE/DCN
                E E3+ALL/DCN
L113       1884 S E2 OR 1860/DRN
                E HYDROXYETHYL CELLULOSE/DCN
                E E3+ALL/DCN
L114       1259 S E2 OR 1859/DRN
                E HYDROXYPROPYLMETHYL CELLULOSE/DCN
                E HYDROXYPROPYL METHYLCELLULOSE/DCN
                E E3+ALL/DCN
L115       1117 S E2
                E SODIUM CARBOXYMETHYL CELLULOSE/DCN
                E E3+ALL/DCN
L116        608 S E2
                E METHYL ACRYLATE/DCN
                E ACRYLATE/DCN
L117         89 S L108 AND L112-L116
L118        331 S L109-L111,L117
L119         19 S L118 AND ?IMPLANT?
L120         12 S L119 AND (B12-M10? OR C12-M10?)/MC
L121         16 SEA L119 AND R05?/M0,M1,M2,M3,M4,M5,M6
L122          2 S L119 AND A12-V02/MC
L123         19 S L119-L122
L124         11 S L118 AND A61F002/IC,ICM,ICS,ICA,ICI
L125         25 S L123,L124
L126         12 S L125 AND (CATTLE OR COW OR CALF OR ANIMAL OR VETERIN? OR SHEE
L127          6 S L125 AND (RUMINANT? OR LIVESTOCK)
L128         15 S L126,L127
L129         10 S L125 NOT L128
```

FILE 'WPIDS' ENTERED AT 16:48:23 ON 25 MAY 2000

=> d all abeq tech tot l128

L128 ANSWER 1 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-561800 [47] WPIDS
DNC C1999-163735
TI Liquid polymeric compositions for controlled drug release, containing **lactide-glycolide** copolymer and solvents, providing reliable long term release of e.g. antiparasitic agents.
DC A23 A96 B07
IN CHERN, R T; ZINGERMAN, J R
PA (MERI) MERCK & CO INC
CYC 85
PI WO 9947073 A1 19990923 (199947)* EN 42p A61F002-02 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU ZA
AU 9930100 A 19991011 (200008) A61F002-02 <--
ADT WO 9947073 A1 WO 1999-US5938 19990318; AU 9930100 A AU 1999-30100 19990318
FDT AU 9930100 A Based on WO 9947073
PRAI GB 1998-15801 19980721; US 1998-79574 19980319
IC ICM **A61F002-02**
ICS A61K009-50; B01J013-02; B32B005-16
AB WO 9947073 A UPAB: 19991116
NOVELTY - Liquid polymeric compositions for controlled release of hydrophobic drugs contain a polymer and a lipophilic solvent.
DETAILED DESCRIPTION - A liquid composition for the controlled release of hydrophobic active agents (I) comprises:
(a) 1-30 (preferably 1-10, especially 5-10) % (I);
(b) 1-20 (preferably 1-10, especially 5-10) % of a poly(lactide-coglycolide) copolymer, the weight ratio of (b) to (a) being 1:1 or less; and
(c) a mixture of hydrophilic and lipophilic solvents in a volume ratio of 80:20-5:95 (preferably 63:35-35:65).
Alternatively the composition comprises:
(a) 1-30% (I);
(b) 1-20% of at least one biologically acceptable polymer, the weight ratio of (b) to (a) being 1:1 or less; and
(c) at least one lipophilic solvent (optionally mixed with at least one hydrophilic solvent), where the volume ratio of hydrophilic to lipophilic solvents is 80:20 to 0:100 volume ratio and/or the lipophilic solvent is present in an amount of at least 16.5 wt.%;
INDEPENDENT CLAIMS are also included for methods for the controlled release of (I) in an **animal** (including humans), involving injecting the above compositions.
USE - The compositions form a film encapsulated liquid e.g. in situ and/or achieve a long-term sustained release in a patient or host such as plasma profiles showing high efficacy. The in situ formed film coated or encapsulated liquid **implant** can functioning as delivery system for (I) to tissues adjacent to or distant from the **implant** site.
(I) include e.g. insecticides, acaricides, parasiticides, anthelmintics, growth enhancers, non-steroidal antiinflammatory agents, estrogens, progestins and androgens.
ADVANTAGE - The formulation tends to stay as a film-coated (encapsulated) liquid, rather than forming a solid, gel or masses. Efficient sustained release can be provided for long periods, e.g. 1-12 months or even longer, without 'bursts' of drug release.
Dwg.0/5
FS CPI
FA AB; DCN
MC CPI: A12-V01; B01-A02; B01-C03; B01-C04; B02-Z; B04-C03D; B06-E05; B07-A02A; B07-A04; B07-D03; B07-D08; B10-D01; B10-E04C;

B12-M10

TECH UPTX: 19991116

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Agents: (I) is selected from fipronil, avermectins, ivermectins, eprinomectin, milbemycins, nodulisporic acid (or derivatives), **estradiol benzoate**, **trenbolone acetate**, pregesterone or norethisterone.

TECHNOLOGY FOCUS - POLYMERS - Preferred Composition: The lactide to glycolide ratio of the poly(lactide-co-glycolide) copolymer is 95:5-50:50 (preferably 75:25-65:35). The hydrophilic solvent is glycerol formal, glycofural, N-methyl-pyrrolidone, 2-pyrrolidone, isopropylidene glycerol and/or di(propylene glycol) methyl ether. The solvent mixture is especially glycerol formal and triacetin in a volume ratio of 65:35 to 35:65.

L128 ANSWER 2 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-457900 [38] WPIDS
DNC C1999-134346
TI Sustained release **implants** have film coating of water soluble pore forming agent useful e.g. for releasing biologically active agents.
DC A11 A14 A25 A96 B01 B07 C03 C07 D22
IN LEE, C E; LEE, J; PUSHPALA, S
PA (AMHP) AMERICAN HOME PROD CORP
CYC 83
PI WO 9930685 A1 19990624 (199938)* EN 49p A61K009-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9918242 A 19990705 (199948) A61K009-00
US 6022554 A 20000208 (200014) A61F002-00 <--
ADT WO 9930685 A1 WO 1998-US26533 19981214; AU 9918242 A AU 1999-18242 19981214; US 6022554 A US 1997-990367 19971215
FDT AU 9918242 A Based on WO 9930685
PRAI US 1997-990367 19971215
IC ICM **A61F002-00**; A61K009-00
ICS **A61F002-10**; A61K009-28; A61K009-50
AB WO 9930685 A UPAB: 19990922
NOVELTY - Sustained-release **implant** comprises:
(i) a biologically active agent (I); and
(ii) a film coat comprising a mixture of an insoluble polymer (III) and a polyethylene glycol (II) or a water soluble pore forming agent (IV) to regulate the release of (I).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a formulation comprising at least one water insoluble polymer (III') and (II) or (IV).
USE - For sustained release subcutaneous **implants**, releasing biologically active agent at a constant rate over a prolonged period of time.
ADVANTAGE - The coating method allows a simple way of extending the duration of an **implant** without dramatic re-formulation of existing products and excessive costs. By varying the amount of pore-forming agent the duration of the **implant** may be tailored to the desired target. The porous film increases the useful life of the **implant**.
DESCRIPTION OF DRAWING(S) - The figure shows the in vitro diffusion of **trenbolone acetate** (TBA) and **estradiol** (EB) through various polymers.
Dwg.1/13
FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; B01-A02; B04-C03B; B04-C03C; B11-C04A; **B12-M10A**; B14-D01; B14-D01B; C01-A02; C04-C03B; C04-C03C; C11-C04A;

C12-M10A; C14-D01; C14-D01B; D09-C

TECH UPTX: 19990922

TECHNOLOGY FOCUS - POLYMERS - (III) is water-insoluble and comprises **cellulose** ethyl ether, poly(m)ethacrylate or polytrimethylammonioethylmethacrylate. (IV) is polyethylene glycol, polypropylene glycol, sugar, salt, poloxamer or polyvinylalcohol.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The molecular weight of (II) is 200-20000, preferably 8000. The film coat comprises 10-50% dry weight (II). (III) is water-insoluble and comprises **cellulose** ethyl ether, poly(m)ethacrylate or polytrimethylammonioethylmethacrylate. (IV) is polyethylene glycol, polypropylene glycol, sugar, salt, poloxamer or polyvinylalcohol.

TECHNOLOGY FOCUS - PHARMACEUTICALS - (I) is a steroid hormone, preferably an estrogen derivative in combination with a progestogen and/or an androgen. Alternatively, (I) is a steroid hormone used in an amount to promote **livestock** weight gain, preferably **estradiol benzoate** and **trenbolone acetate** and the thickness of the film coat is 5-50microm.

L128 ANSWER 3 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1997-351376 [33] WPIDS
DNC C1997-113576
TI Sustained-release formulation of **animal** growth hormone - comprising **implantable** pellets coated with biodegradable polymer and poloxamer.
DC A23 A96 B04 C03
IN JUNG, M; KIM, A; KIM, N; CHUNG, M H; KIM, A R; KIM, N J
PA (GLDS) LG CHEM LTD
CYC 8

PI	AU 679150	B	19970619 (199733)*		25p	A61K038-27
	DK 9700034	A	19970711 (199740)			A61K038-27
	JP 09194348	A	19970729 (199740)		7p	A61K009-52
	CA 2194610	A	19970711 (199747)			A61K038-27
	US 5744163	A	19980428 (199824)		9p	A61K009-14
	KR 97058724	A	19970812 (199837)			A61K038-27
	BR 9605907	A	19980818 (199839)			A61K038-27
	JP 2896355	B2	19990531 (199927)		7p	A61K009-22
	CA 2194610	C	19990511 (199937)	EN		A61K038-27
	MX 9605929	A1	19980501 (200007)			A61K037-36

ADT AU 679150 B AU 1996-71725 19961112; DK 9700034 A DK 1997-34 19970110; JP 09194348 A JP 1997-1883 19970109; CA 2194610 A CA 1997-2194610 19970108; US 5744163 A US 1996-749912 19961113; KR 97058724 A KR 1996-341 19960110; BR 9605907 A BR 1996-5907 19961209; JP 2896355 B2 JP 1997-1883 19970109; CA 2194610 C CA 1997-2194610 19970108; MX 9605929 A1 MX 1996-5929 19961128
FDT AU 679150 B Previous Publ. AU 9671725; JP 2896355 B2 Previous Publ. JP 09194348
PRAI KR 1996-341 19960110
IC ICM A61K009-14; A61K009-22; A61K009-52; A61K037-36; A61K038-27
ICS A61K009-32; A61K009-58; A61K031-74
AB AU 679150 B UPAB: 19981028
Sustained-release formulation of an **animal** growth hormone comprises a solid pellet containing the hormone and an excipient, the pellet being coated with a film composed of a biodegradable polymer and a poloxamer.

Also claimed is a process for preparing the formulation, comprising directly tabletting a powder mixture of the hormone and excipient and coating the resulting pellet.

The hormone is bovine or porcine **somatotropin**. The formulation contains 20-80 wt.% of the hormone. The biodegradable polymer is **polylactide**, **polyglycolide** or poly(lactide-co-glycolide). The excipient is present in an amount of 20-80 wt.% and is selected from hydrophilic materials, especially polyethylene glycol, dextran, pectin, alginic acid, **cellulose** and gelatin, and hydrophobic materials, especially paraffin wax, carnauba wax, beeswax,

zein and **ethylcellulose**. The ratio of biodegradable polymer to poloxamer is 7:3 to 9:1.

ADVANTAGE - The formulation continuously releases an effective and steady amount of the hormone over a period of more than a week when **implanted** in an **animal**, e.g. **pig** or **cow**.

Dwg.0/3

FS CPI
FA AB; DCN
MC CPI: A09-A07; A12-V; B04-C03D; C04-C03D; B04-J05J; C04-J05J; B11-C04A; C11-C04A; **B12-M10A**; **C12-M10A**; B12-M11D; C12-M11D

L128 ANSWER 4 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1994-064828 [08] WPIDS
CR 1995-138882 [18]; 1995-206208 [27]; 1995-240004 [31]; 1997-350192 [32]; 1998-050933 [51]; 1998-238660 [20]
DNN N1994-050848 DNC C1994-029045
TI Growth promotion in **animals** - by administration of microparticles of steroid in a polymeric matrix.
DC B01 B07 C03 C07 D22 P32
IN LEWIS, D H
PA (STOL-N) STOLLE RES & DEV
CYC 1
PI US 5288496 A 19940222 (199408)* 11p A61F013-00
ADT US 5288496 A US 1990-523249 19900515
PRAI US 1990-523249 19900515
IC ICM A61F013-00
AB US 5288496 A UPAB: 19980528

Promoting growht in **animals** comprises admin. of an injectable, biodegradable compsn. comprising microparticles, the microparticles comprising a steroid growth promoter within a polymeric matrix.

Pref., the polymeric matrix may be poly-d,l-lactic acid, poly-L-lactic acid, polyglycolin acid, copolymers of mixed d,e-lautic and glycolin acid, copolyoxalates, polycaprolactone, poly (lactic and caprolactone), poly(glycolin acid-caprolactone), casein, albumin or waxes. The microparticles may be loaded with 1-75 wt.% of growth promoter based on the polymeric matrix wt. The microparticle size suitably ranges from 1 to 250 microns. THe compsn. may be in a liquid injection vehicle e.g. physiological saline, or an aq. soln. of carboxymethyl **cellulose** with a surfactant admin. may be by the intravenous, intramuscular or subintaneous route.

USE/ADVANTAGE - The microparticles may be used to promote growth in e.g. **cattle**, **sheep**, migs, fowl and rabbits. The microparticles provide an injectable system which prevents the loss of dose during treatment which often occurs with solid pellet **implants**; the ability to mix microparticles contg. different drugs and the ability to programme release to give faster rates of drug release as the **animal** grows larger further, the method provides the ability to define a unique blood hormone profile for the **animal** and a multiple hormone delivery system which provides fluid doses of desired growth promoter, then eliminating a need for continue **implant** treatments.

Dwg.0/1

FS CPI GMPI
FA AB; DCN
MC CPI: B01-A02; B01-C05; B04-C03D; B14-E11; B14-S12; C01-A02; C01-C05; C04-C03D; C14-E11; C14-S12; D09-C

L128 ANSWER 5 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1991-247073 [34] WPIDS
DNC C1991-107213
TI Compsns. contg. stigmasta-4-en-3-one - to treat androgen-dependent diseases e.g. prostate hyperplasia or carcinoma, or testicular tumour.
DC B01
IN STREBER, A S
PA (BOOT) BOOTS PHARMA GMBH; (KANO-N) KANOLDT ARZNEIMITTEL GMBH

CYC 12
PI EP 442350 A 19910821 (199134)*
R: AT BE CH DE FR GB IT LI NL SE
DE 4004920 C 19910919 (199138)
JP 04211013 A 19920803 (199237) 5p A61K031-575
US 5264428 A 19931123 (199348) 4p A61K031-56
EP 442350 B1 19940608 (199422) DE 6p A61K031-575
R: AT BE CH DE FR GB IT LI NL
DE 59101818 G 19940714 (199428) A61K031-575
ADT EP 442350 A EP 1991-101516 19910205; DE 4004920 C DE 1990-4004920 19900216; JP 04211013 A JP 1991-20960 19910214; US 5264428 A Cont of US 1991-656783 19910215, US 1992-876131 19920429; EP 442350 B1 EP 1991-101516 19910205; DE 59101818 G DE 1991-501818 19910205, EP 1991-101516 19910205
FDT DE 59101818 G Based on EP 442350
PRAI DE 1990-4004920 19900216
REP 3.Jnl.Ref; DE 3827953; JP 61148111; JP 61148196; PL 95726; 04Jnl.Ref
IC ICM A61K031-56; A61K031-575
ICS A61K031-57; C07J009-00
AB EP 442350 A UPAB: 19940524
Compsns. contg. stigmasta-4-en-3-one (1) are new. Pref. compsns. also contain lactose and/or maltodextrin, and/or a **cellulose** prepn., esp. calcium carboxymethyl **cellulose**, and the content of (1) is 2-80 mg.

USE/ADVANTAGE - (1) are antiandrogens used to treat androgen-dependent diseases e.g. carcinoma of the prostrate, testicular tumours and prostrate hyperplasia (claimed). The dose of (1) required is lower than known anti-androgen prepns., and hence there are fewer side effects. The compsn. may be administered orally as tablets, capsules etc., or injected as an oily or thinned alcoholic soln. The daily dose is e.g. 20-80 mg.

In an example, the effect of (1) was compared with that of an anti-androgenic extract of stinging nettle root (Radix urticae). The active agents were given to castrated male rates with **testosterone implants**, and the wt. of the prostate was determined. In control rats, the wt. of the prostate increased from 97.6-449.5 mg when 10% **testosterone** was included in the **implant**. With the same amt. of **testosterone** 10 mg/kg nettle extract reduced the increase to 354 mg and 0.16 mg/kg (1) reduced the increase to 360 mg. @(7pp Dwg.No.0/0)
0/0
FS CPI
FA AB; DCN
MC CPI: B01-C09; B12-G04B; B12-G07
ABEQ DE 4004920 C UPAB: 19930928
The use of stigmasta-4-ene-3-one of formula (I) or stigmasta-4, 22-diene-3-one (II) is claimed for the treatment of androgen-dependent disorders, namely prostate carcinoma, testicular tumours and benign prostate hyperplasia.

USE/ADVANTAGE - When used for treating benign prostate hyperplasia, (I) and (II) significantly reduce prostate wt. and are effective at lower concns. than known drugs based on plant extracts.

Dose is 20-80 (20-60) mg/d, administered orally, intramuscularly or subcutaneously.

In an example, male Sprague Dawley rats were first given gonadectomies and were then given **implants** that discharged a constant amt. of **testosterone** into their bloodstream. This was followed by a course of the test substance, beginning on the day of the operation and lasting 10 days. The **animals** were sacrificed and the prostate wt. was measured. For rats with **implants** that discharged 50% of normal **testosterone** levels, the results were as follows. Control ats weighing 236-8 g on average had a prostate wt. of 596-2 mg. This compares with 484 mg for rats weighing 299.5 g, which were given 0.32 mg/kg (I), and 403 mg for rats weighing 307.5 g, which were given 20 mg/kg nettle root extract. @(5pp)@
ABEQ US 5264428 A UPAB: 19940120
Method comprises admin. of an effective amt. of stimanta-4-en-3-one of

formula (I).
USE/ADVANTAGE - For treating androgen dependent carriers such as prostate carcinoma and/or testicular tumours and prostrate hyperplasia (claimed). No side effects such as inhibition of permiogenesis, inhibition of libido and potency and increase in weight as well as gynacomastia occur.
Dwg.0/0
ABEQ EP 442350 B UPAB: 19940722
Use of 4-stigmasten-3-one or 4,22-stigmastadiene-3-one to produce a medicament for treating androgen-related diseases with the exception of hair loss.
Dwg.0/0

L128 ANSWER 6 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1991-245428 [33] WPIDS
DNN N1991-187248 DNC C1991-106575
TI Device for sustained admin. of steroid hormone - to promote wt. gain in **livestock**, comprises hydrophilic polymer, solubilising agent and encapsulating rate controlling membrane.
DC A25 A96 B01 B07 C03 D22 P32
IN LEE, J C; RUNKEL, R A
PA (SYNT) SYNTEX (USA) INC
CYC 1
PI US 5035891 A 19910730 (199133)*
ADT US 5035891 A US 1989-398106 19890824
PRAI US 1987-105149 19871005; US 1989-398106 19890824
IC A61F013-00
AB US 5035891 A UPAB: 19930928
A reservoir device for the sustained admin. of a steroid hormone useful for promoting wt. gain in **livestock** comprises (a) a pellet or number of pellets, it or each comprising (i) a suitable amount of steroid hormone, (ii) a solid hydrophilic polymer in an amt. sufficient to cause swelling of the device by osmotic pressure, and (iii) an ionic surfactant having an 8-22C aliphatic chain to act as a solubilising agent, in an amt. sufficient to maintain an effective concn. of the steroid in soln. within the device; and (b) a sufficient amt. of a non-porous, rate-controlling membrane which completely encapsulates the pellet(s), the membrane being prepd. from an aliphatic or aromatic polyurethane, a silicone rubber, a polyethylene-vinyl acetate copolymer or a polystyrene-butadiene copolymer, the membrane being permeable to water and the steroid but impermeable to the solubilising agent and the hydropholic polymer; the device being suitable for subcutaneous **implantation**.
0/0
FS CPI GMPI
FA AB; DCN
MC CPI: A04-B03; A04-G07; A05-G01E; A06-A00E3; A12-V; A12-V01; A12-W04; A12-W05; B01-A02; B01-C04; B01-C05; B04-C03B; B04-C03C; B04-C03D; B11-C04A; B12-G04C; B12-L09; B12-M09; **B12-M10A**; B12-M11D; C01-A02; C01-C04; C01-C05; C04-C03B; C04-C03C; C04-C03D; C11-C04A; C12-G04C; C12-L09; C12-M09; **C12-M10A**; C12-M11D; D09-C04

L128 ANSWER 7 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1991-094698 [14] WPIDS
CR 1998-397951 [34]; 1999-152710 [13]
DNN N1991-073185 DNC C1991-040497
TI Oral osmotic delivery device - having semi-permeable wall surrounding beneficial agent and hydrophilic polymer with passageway in wall.
DC A96 B07 C03 P32 P34
IN BARCLAY, B L; CHILDERS, J D; PLACE, V A; WONG, P S; WRIGHT, J; WONG, P; WONG, P S L
PA (ALZA) ALZA CORP; (BARC-I) BARCLAY B L
CYC 24
PI CA 2020955 A 19910115 (199114)* 40p
WO 9101130 A 19910207 (199114)
RW: AT BE CH DE DK ES FR GB IT LU NL SE
W: AU FI JP KR NO US

PT 94664 A 19910418 (199118)
AU 9060476 A 19910222 (199120)
ZA 9005429 A 19910424 (199122)
US 5021053 A 19910604 (199125) 13p
US 5053032 A 19911001 (199142) 12p
FI 9200164 A 19920114 (199215)
EP 482075 A 19920429 (199218) EN 48p
R: AT BE CH DE DK ES FR GB IT LI LU NL SE
NO 9105043 A 19920113 (199218)
AU 633340 B 19930128 (199311) A61K009-22
NZ 234447 A 19930326 (199316) A61K009-22
NZ 243890 A 19930326 (199316) A61K009-22
JP 05502215 W 19930422 (199321) 16p A61K009-00
EP 482075 B1 19940504 (199418) EN 32p A61K009-22
R: AT BE CH DE DK ES FR GB IT LI LU NL SE
DE 69008727 E 19940609 (199424) A61K009-22
ES 2052263 T3 19940701 (199429) A61K009-22
IE 62717 B 19950222 (199519) A61K009-22

ADT CA 2020955 A CA 1990-2020955 19900711; ZA 9005429 A ZA 1990-5429 19900711; US 5021053 A US 1989-380229 19890714; US 5053032 A US 1990-633590 19901221; EP 482075 A EP 1990-911340 19900711; AU 633340 B AU 1990-60476 19900711; NZ 234447 A NZ 1990-234447 19900711; NZ 243890 A NZ 1990-243890 19900711; JP 05502215 W JP 1990-510587 19900711, WO 1990-US3882 19900711; EP 482075 B1 EP 1990-911340 19900711, WO 1990-US3882 19900711; DE 69008727 E DE 1990-608727 19900711, EP 1990-911340 19900711, WO 1990-US3882 19900711; ES 2052263 T3 EP 1990-911340 19900711; IE 62717 B IE 1990-2525 19900711

FDT EP 482075 A Based on WO 9101130; AU 633340 B Previous Publ. AU 9060476, Based on WO 9101130; NZ 243890 A Div ex NZ 234447; JP 05502215 W Based on WO 9101130; EP 482075 B1 Based on WO 9101130; DE 69008727 E Based on EP 482075, Based on WO 9101130; ES 2052263 T3 Based on EP 482075

PRAI US 1989-380229 19890714; US 1990-633590 19901221

REP US 4327725

IC ICM A61K009-00; A61K009-22
ICS **A61F002-00**; A61K009-24; A61M035-00

AB CA 2020955 A UPAB: 19990331
An osmotic device for the controlled delivery of a beneficial agent to an oral cavity of an **animal** over an extended delivery period is claimed. The device includes a wall surrounding and forming a compartment contg. (i) a layer of a dose of the beneficial agent and a gelling agent. The beneficial agent is insoluble to very soluble in the aq. fluid of the mouth and (ii) a layer of a hydrophilic polymer and a passagway in the wall. The wall is formed of a semipermeable material which is (i) permeable to aq. fluid and (ii) impermeable to the hydrophlic polymer. The device is comfortably retained in the oral cavity fot the extended delivery period, and a mechanism for signalling the **animal** when the dose of beneficial agent has been delivered from the device.

Pref. the wall contains a translucent **cellulose** polymer. The gelling agent may be eg. ocacia, agar-agar, calcium carrageenan, alginic acid, algin, agarose powder, collagen, colloidal magnesium, silicate, colloidal SiO2, cross-linked polyacrylic acid, PVP, sodium CMC, hydroxyethyl **cellulose**, hydroxypropyl **cellulose**, hydroxypropyl **methylcellulose** (HPMC) polyethylene oxide, pectin, gelatin or calcium silicate.

USE/ADVANTAGE - The agent is released through the passagway at a rate controlled by the permeability of the wall, the osmotic pressure gradient across the wall and the rate of expansion of the driving hydrophilic polymer over a prolonged delivery period. The device can be used for deliveing e.g. bystatin, chlorhexidene ibuprofen, nicotine base, NaF, pilocarpine, retin A, glucocorticosteroids, **testosterone**, oestrogen, nitroglycerine, captopril or clonidine.

Dwg.4/5

FS CPI GMPI

FA AB; GI; DCN

MC CPI: A12-V01; A12-W05; B01-A01; B01-C05; B02-N; B03-A; B04-B02D1; B04-B04A6; B04-C02A; B04-C03; B05-A01B; B05-B02C; B07-H; B10-A05;

B10-A17; B10-C04C; B12-M10A; C01-A01; C01-C05; C02-N; C03-A; C04-B02D1; C04-B04A6; C04-C02A; C04-C03; C05-A01B; C05-B02C; C07-H; C10-A05; C10-A17; C10-C04C; C12-M10A

ABEQ US 5021053 A UPAB: 19930928

An osmotic device for the delivery of a beneficial agent in to an oral cavity over an extended period, including a wall surrounding and forming a compartment contg. (i) a layer of the beneficial agent and a gelling agent, the beneficial agent may be insol to very soluble in an exterior aq. fluid, and (ii) a layer of a hydrophilic polymer, and a passageway in the semipermeable wall communicating with the layer of beneficial agent in the compartment and with the exterior device. The wall is formed of a material which is (i) permeable to aq. fluid, and (ii) impermeable to hydrophilic polymer.

The device also comprises a mechanism for signalling the **animal**, having a contrast in the colours of the beneficial agent layer and the hydrophilic polymer layer. The semipermeable wall is sufficiently transparent to permit visual inspection of the beneficial agent present in the compartment, and a mark to indicate when a predetermined percentage of the drug dose has been delivered to the oral cavity.

USE - The device is used to deliver many difficult to deliver beneficial agents. @(13pp)@

ABEQ US 5053032 A UPAB: 19930928

Osmotic device for the controlled oral administration of drugs or beneficial compsns. to human patients comprises a container that fits easily in the mouth, having an orifice to the interior of the container, where a pharmaceutical or nutrient compsn. is retained behind a hydrophilic membrane that swells in the saliva and allows the active components to permeate through, into the mouth. The container is essentially transparent and opt. calibrated, so that the patient can observe the amt. of active compsn. remaining.

USE - The prods. are suitable for the administration of a wide range of pharmaceuticals, antifungal agents, nutrients etc.

ABEQ JP 05502215 W UPAB: 19931114

An osmotic device for the controlled delivery of a beneficial agent to an oral cavity of an **animal** over an extended delivery period is claimed. The device includes a wall surrounding and forming a compartment contg. (i) a layer of a dose of the beneficial agent and a gelling agent. The beneficial agent is insoluble to very soluble in the aq. field of the mouth and (ii) a layer of a hydrophilic polymer and a passageway in the wall. The wall is formed of a semipermeable material which is (i) permeable to aq. fluid and (ii) impermeable to the hydrophilic polymer. The device is comprised in the oral cavity for the extended delivery period, and a mechanism for signalling the **animal** when the dose of beneficial agent has been delivered from the device.

Pref. the wall contains a translucent **cellulose** polymer. The gelling agent may be e.g. acacia, agar-agar, calcium carrageenan, alginic acid, algin, agarose powder, collagen, colloidal magnesium silicate, colloidal SIO2, cross-linked polyacrylic acid, PVP, sodium CMC, hydroxyethyl **cellulose**, hydroxypropyl **cellulose**, hydroxypropyl **methylcellulose** (HPMC), polyethylene oxide, pectin, gelatin or calcium silicate.

USE/ADVANTAGE - The agent is released through the passageway at a rate controlled by the permeability of the wall, the osmotic pressure gradient across the wall and the rate of expansion of the driving hydrophilic polymer over a prolonged delivery period. The device can be used for delivering e.g. nystatin, chlorhexidene, ibuprofen, nicotine base, NaF, pilocarpine, retin A, glucocorticosteroids, **testosterone**, oestrogen, nitroglycerine, captopril or chloridine. Dwg.0/0

ABEQ EP 482075 B UPAB: 19940622

A osmotic device for the controlled delivery of a beneficial agent to an oral cavity of an **animal** over an extended delivery period, including a wall surround and forming a compartment containing (i) a layer of a dose of the beneficial agent and a gelling agent, the beneficial agent being insoluble to very soluble in an exterior aqueous fluid present

in the oral cavity, and (ii) a layer of a hydrophilic polymer, and a passageway in the semipermeable wall communicating with the layer of beneficial agent in the compartment and with the exterior of the device, the wall being formed of a semipermeable material which is (i) permeable to the passage of the aqueous fluid and (ii) substantially impermeable to the passage of the hydrophilic polymer, the device having a size and shape suitable for comfortably retaining the device in the oral cavity for the extended delivery period, the device having a mechanism for signalling the **animal** when the dose of beneficial agent has been delivered from the device.
Dwg.1/5

L128 ANSWER 8 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1990-320061 [42] WPIDS
DNC C1990-138542
TI Controlled release delivery device - for macromolecular proteins, e.g. **somatotropin**, releases protein similar to series of injections.
DC A96 B04 B07 C03 D13
IN MILLER, L F; SIVARAMAKRISHNAN, K N; MILLER, L; SIVARAMAKR, K N
PA (PITM) PITMAN MOORE INC
CYC 17
PI WO 9011070 A 19901004 (199042)*
RW: AT BE CH DE DK ES FR GB IT LU NL SE
W: AU JP NO
AU 9052792 A 19901022 (199104)
EP 463061 A 19920102 (199202)
R: AT BE CH DE ES FR GB IT LI LU NL SE
NO 9103649 A 19910916 (199204)
JP 04504122 W 19920723 (199236) 12p A61K009-00
AU 634529 B 19930225 (199315) A61K009-52
EP 463061 B1 19930609 (199323) EN 20p A61K009-52
R: AT BE CH DE DK ES FR GB IT LI LU NL SE
US 5219572 A 19930615 (199325) 11p A23K001-18
DE 69001898 E 19930715 (199329) A61K009-52
ES 2042292 T3 19931201 (199401) A61K009-52
ADT WO 9011070 A WO 1990-1340 19900313; EP 463061 A EP 1990-905065 19900313; JP 04504122 W JP 1990-505092 19900313, WO 1990-US1340 19900313; AU 634529 B AU 1990-52792 19900313; EP 463061 B1 EP 1990-905065 19900313, WO 1990-US1340 19900313; US 5219572 A Cont of US 1989-324740 19890317, US 1991-734120 19910725; DE 69001898 E DE 1990-601898 19900313, EP 1990-905065 19900313, WO 1990-US1340 19900313; ES 2042292 T3 EP 1990-905065 19900313
FDT JP 04504122 W Based on WO 9011070; AU 634529 B Previous Publ. AU 9052792, Based on WO 9011070; EP 463061 B1 Based on WO 9001340; DE 69001898 E Based on EP 463061, Based on WO 9011070; ES 2042292 T3 Based on EP 463061
PRAI US 1989-324740 19890317
REP EP 37740; US 2738303; US 4590062; US 4666704; US 4837381; WO 8801506; WO 8801512; WO 9001329
IC ICM A23K001-18; A61K009-52
ICS A61K009-22; A61K009-54; A61K009-56; A61K009-58; A61K009-60; A61K009-62; A61K009-64; A61K037-02; A61K037-36; A61K037-48; A61K039-00
AB WO 9011070 A UPAB: 19930928
Controlled release delivery device for delivering macromolecular proteins (I) to an **animal** comprises an inner compartment contg. non-uniform beadlets made of a rupturable wax shell completely surrounding a core matrix contg. (I) and a water-sol. outer capsule completely surrounding the inner compartment.

(I) may be an enzyme, enzyme inhibitor, antibody, antigen, or interferon, insulin, prolactin, somatomedin, somatostatin, interleukin, somatocrinin or **somatotropin**.

USE/ADVANTAGE - The method is esp. useful for delivery of **somatotropin** to **animals** for promoting growth and increasing feed utilisation efficiency. The device controls the manner and timing of delivery while maintaining the stability and bioactivity of (I). The outer capsule dissolves in about 1-6 hrs. thus exposing the beadlets

directly to body fluids. Each beadlet separately ruptures over a prolonged period depending on the wax shell's parmeters, such as thickness, and type. This method provides delivery of (I) over the life of the **implant**, similar to a series of injections. For delivery of **somatotropin**, a mixt. of beadlets designed to deliver 0.1-20 (1-10) mg/**animal**/day over 1-14 days is incorporated into the outer capsule.
0/2

FS CPI
FA AB; DCN
MC CPI: A12-V; A12-V01; A12-W05; B02-V03; B04-B01C; B04-B02C; B04-B02D2; B04-B02D4; B04-B04A6; B04-B04C; B04-B04J; B04-C01; B04-C02A2; B04-C03A; B04-D02; B11-C04A; B12-L09; **B12-M10A**; B12-M11C; C02-V03; C04-B01C; C04-B02C; C04-B02D2; C04-B02D4; C04-B04A6; C04-B04C; C04-B04J; C04-C01; C04-C02A2; C04-C03A; C04-D02; C11-C04A; C12-L09; **C12-M10A**; C12-M11C; D03-G
ABEQ EP 463061 B UPAB: 19931115
A controlled release delivery device for delivering macromolecular proteins to an **animal** over a prolonged period, characterised in that it comprises: an inner compartment which contains a plurality of non-uniform beadlets, the beadlets comprising a rupturable wax shell which completely surrounds a core matrix containing the macromolecular protein; and a water- soluble outer capsule completely surrounding the inner compartment.
Dwg.0/2
ABEQ US 5219572 A UPAB: 19931116
Controlled release delivery device comprises (a) beadlets having non-uniform rupture times, each comprising core matrix contg. macromolecular protein with a rupturable wax shell completely surrounding it; and (b) a water-soluble outer capsule completely surrounding (a).
Core matrix opt. includes excipients, stabilisers, binders, surfactants and/or preservatives. Beadlet comprises a pellet, tablet or microcapsule.
USE - For **implantation** in an **animal**, so that **somatotropin** (or other macromolecular protein) is administered over a prolonged period.
Dwg.0/2

L128 ANSWER 9 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1990-187240 [25] WPIDS
CR 1996-087531 [09]
DNN N1990-145623 DNC C1990-081169
TI Delivery of beneficial agent to an environment - in which fluid from the environment expands a member to deliver the agent.
DC B07 P32 P34
IN CORTESE, R; ECKENHOFF, J B; MAGRUDER, J A; PEERY, J R; WRIGHT, J C
PA (ALZA) ALZA CORP
CYC 21
PI EP 373867 A 19900620 (199025)* 23p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
AU 8942478 A 19900621 (199031)
NO 8904810 A 19900709 (199033)
JP 02184619 A 19900719 (199035)
ZA 8907706 A 19900725 (199035)
DK 8906245 A 19900614 (199036)
US 5034229 A 19910723 (199132) 17p
US 5037420 A 19910806 (199134) 17p
US 5057318 A 19911015 (199144) 17p
US 5059423 A 19911022 (199145) 17p
US 5110596 A 19920505 (199221) 17p
US 5135523 A 19920804 (199234) 17p A61K009-22
US 5174999 A 19921229 (199303) 17p A61K009-22
AU 633514 B 19930204 (199312) A61M007-00
EP 373867 B1 19931027 (199343) EN 23p A61M031-00
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
DE 68910290 E 19931202 (199349) A61M031-00

ES 2045474	T3	19940116	(199407)		A61M031-00
NO 174878	B	19940418	(199419)		A61M037-00
US 5320616	A	19940614	(199423)	17p	A61K009-22
CA 1331328	C	19940809	(199434)		A61M031-00
JP 2532692	B2	19960911	(199641)	17p	A61K009-00
US 5630808	A	19970520	(199726)	17p	A61K009-22
US 5714160	A	19980203	(199812)	16p	A61K009-52
KR 132212	B1	19980411	(200010)		A61M031-00

ADT EP 373867 A EP 1989-312940 19891212; JP 02184619 A JP 1989-300980 19891121; ZA 8907706 A ZA 1989-7706 19891011; US 5034229 A US 1988-283359 19881213; US 5037420 A US 1990-513328 19900420; US 5057318 A US 1990-513327 19900420; US 5059423 A US 1990-513528 19900423; US 5110596 A US 1988-283359 19881213; US 5135523 A Div ex US 1988-283359 19881213, US 1990-513363 19900420; US 5174999 A Div ex US 1988-283359 19881213, US 1990-512301 19900420; AU 633514 B AU 1989-42478 19891003; EP 373867 B1 EP 1989-312940 19891212; DE 68910290 E DE 1989-610290 19891212, EP 1989-312940 19891212; ES 2045474 T3 EP 1989-312940 19891212; NO 174878 B NO 1989-4810 19891201; US 5320616 A Div ex US 1988-283359 19881213, Cont of US 1990-513369 19900420, US 1991-789241 19911107; CA 1331328 C CA 1989-614335 19890928; JP 2532692 B2 JP 1989-300980 19891121; US 5630808 A Div ex US 1988-283359 19881213, Cont of US 1990-513369 19900420, Cont of US 1991-789241 19911107, US 1994-203967 19940301; US 5714160 A Div ex US 1988-283359 19881213, Cont of US 1990-513361 19900420, US 1996-627169 19960403; KR 132212 B1 KR 1989-15892 19891102

FDT US 5135523 A Div ex US 5034229; US 5174999 A Div ex US 5034229; AU 633514 B Previous Publ. AU 8942478; DE 68910290 E Based on EP 373867; ES 2045474 T3 Based on EP 373867; NO 174878 B Previous Publ. NO 8904810; US 5320616 A Div ex US 5034229; JP 2532692 B2 Previous Publ. JP 02184619; US 5630808 A Div ex US 5034229, Cont of US 5320616; US 5714160 A Div ex US 5034229

PRAI US 1988-283359 19881213; US 1990-513328 19900420; US 1990-513327 19900420; US 1990-513528 19900423; US 1990-513330 19900420; US 1990-513363 19900420; US 1990-512301 19900420; US 1990-513369 19900420; US 1991-789241 19911107; US 1994-203967 19940301; US 1990-513361 19900420; US 1996-627169 19960403

REP GB 2179252; US 3732865; US 3995632; US 4612008

IC ICM A61K009-00; A61K009-22; A61K009-52; A61M007-00; A61M031-00; A61M037-00

ICS A23K001-18; A61D007-00; **A61F002-00**; A61F013-00; A61K037-26; A61K037-36

AB EP 373867AN 0 UPAB: 20000228

Beneficial agent (20) is accommodated within a receptacle (18), in a portion (16) having fluid impermeable walls (12a) and an exit (13) through which the agent (20) can be dispensed into the environment of use. A second portion (17) of the receptacle has walls (12b) which are capable of permeation by fluids in the environment of use, and contains a substance which expands when subjected to those fluids to exert pressure on and move a fluid impermeable dividing member (27) and so effect ejection of the beneficial agent through the exit (13) into the surrounding environment.

USE/ADVANTAGE - Partic. in the long term delivery of a beneficial drug from a device **implanted** in a human or **animal** body. Can be used to obtain accurately controlled rates of drug delivery while maintaining the integrity of the device and protecting the beneficial agent from deterioration prior to delivery to the environment of use.

Dwg.6/11

FS CPI GMPI

FA AB; GI

MC CPI: B11-C04A; **B12-M10A**

ABEQ US 5034229 A UPAB: 19930928

Dispenser for delivering a beneficial agent to an **animal** comprises a wall surrounding an internal lumen and including a section that permits fluid passage through the wall, and a beneficial agent in the lumen. The agent includes a porcine **somatotropin**, glycerol, Na2PO4, and a surfactant. A hydrogel is also included in the lumen.

ADVANTAGE - Difficult to deliver drugs can be dispensed. @@

ABEQ US 5037420 A UPAB: 19930928

A method for delivering a **somatotropin** agent to an **animal** comprises (a) admitting a dispenser of said agent and an osmopolymer gel and (b) delivering the agent and gel. The dispenser comprises a lumen with a limiting wall with a fluid permeable section, one end inside the other in a fixed fashion which allows replacing the inner section. A **somatotropin** composition comprising 5 nanograms to 20 grams active agent is placed in the lumen with the sep. osmopolymer adj. the permeable section. An exit in the wall allows agent delivery when imbibing fluid passes to it via the gel.

USE - For dosing **livestock** up to slaughter.

ABEQ US 5057318 A UPAB: 19930928

Pharmaceutical/medicinal delivery system comprises an inert plastic tube contg. a reservoir of one or more active components, mounted behind a selectively permeable membrane which allows the passage of aq. media and body fluids but not the beneficial components, osmotic agents, etc.; and a communication channel between the interior and exterior.

USE - When mounted within a body fluid zone, body fluid passes into the chamber contg. the active components, raising the internal pressure so that some of the compsn. is expelled through the communication channel into the surrounding body fluids at a predetermined rate.

ABEQ US 5059423 A UPAB: 19930928

Dispenser for delivering a beneficial agent (I) to an **animal** comprises a wall surrounding an internal lumen comprising a pair of ends in mated contact to form a closed dispenser. The wall has a section (a) that limits passage of fluid into the lumen and a section (b) that permits passage of fluid into it. (I) is in section A of the lumen. An expandable, opt. crosslinked hydrogen which exhibits a 2 to 50 fold volume increase is in section (b). There is an exit passageway in the dispenser for delivering (I) to the **animal**.

USE - For delivering **somatotropin** to a hog. (claimed) @@

ABEQ US 5110596 A UPAB: 19930928

Delivery system for drugs, etc., comprises an **implantable** dispenser which has a wall surrounding an internal lumen. The wall has a pair of ends, one inside the other, with one section limiting passage of fluid through the wall and another permitting passage. The lumen contains 5ng to 20g beneficial agent e.g, drug, protein, peptide, hormone, and expandable hydrogel permitting passage of fluid, and a fluid-impermeable partition between the drug and hydrogel, and exit passageways from the dispenser through which drug is expelled when the hydrogel expands.

ADVANTAGE - Delivery of the agent is maintained over a prolonged period, while it is protected from **animal** body fluids.

ABEQ US 5135523 A UPAB: 19930928

System for delivering a beneficial agent (I) to a fluid environment of use comprises two sections joined together by fusing, by an adhesive or in telescopic engagement.

The first section comprises a reservoir surrounded by a fluid impervious wall. The second section comprises a reservoir surrounded by a fluid permeable wall. An outlet in the first wall allows (I) to be delivered to the environment of use. The second reservoir contains an expandable member to push (I) from the reservoir.

USE - As an **implant** for delivery of drugs to human or **animal** hosts, esp. **cattle** and **pigs**.

5/11

ABEQ US 5174999 A UPAB: 19930928

A dispenser storing beneficial agent and delivering a dose over time comprises a housing with a wall (12a) surrounding a storage space (18) and inhibiting ingress of fluid, and a second wall (12b) surrounding an internal space with a compsn. allowing fluid to enter. 5 ng - 20 g of agent are stored in the dispenser and means in the internal space permit fluid to enter to assist in delivering the agent through an outlet (13).

The first wall may be entirely impermeable to fluid or allow passage of a negligible amount. The dispenser may have a tapered end which can be removed immediately before use to allow fluid entry. The second wall may allow fluid entry to activate an osmotic driving force for expelling the agent from the opposite end of the housing.

USE/ADVANTAGE - For medical or **veterinary** use, is easy to

implant with min. trauma and provides reliable dispensing. (Dwg. 1/11
1/11

ABEQ EP 373867 B UPAB: 19931207
A delivery device (10) for the delivery of a beneficial agent formulation to an environment of use, which device comprises first and second wall portions (12a) and (12b) capable of being assembled together to define a lumen (18) having a first lumen portion defined substantially by said first wall portion (12a) and adapted to accommodate a beneficial agent formulation (21-24) and a second lumen portion defined substantially by said second wall portion (12b) and adapted to accommodate means (25-26) for aiding the delivery of said beneficial agent formulation; exit means (13) formed in said first wall portion and extending between the lumen and environment of use; and a movable, substantially impermeable dividing member (27) extending across the width of the lumen (18) and serving to isolate said beneficial agent formulation from said means for aiding the delivery; characterised in that: (1) said first wall portion (12a) is formed from a material which is substantially impermeable to fluid; and (2) said second wall portion (12b) is formed from a substantially semipermeable material which is permeable to fluid and impermeable to said means for aiding delivery; wherein, in an environment of use, said means for aiding delivery generates an osmotic potential across said second wall portion (12b) thereby causing fluid to enter into the second lumen portion and interact with the means (25-26) for aiding delivery, which latter is thus caused to expand and push the dividing member (27) towards said exit means (13), thereby deliverying the beneficial agent formulation (20-24) from the first lumen portion to the environment of use via said exit means (13).
Dwg.1/11

ABEQ US 5320616 A UPAB: 19940727
A delivery system is provided for delivery of a beneficial agent to a fluid environment of use comprising two wall sections. The first wall section comprises a polymer compsn. limiting passage of up to 1 ml per day of fluid through the wall. The second wall section comprises **cellulosic** polymer compsn. pervious to the passage of fluid surrounded by the two wall section.

A reservoir is formed by the two sections which are fused, adhered or telescopically engaged; and this contains 5 mg to 40 g of fluid sensitive biologically beneficial agent surrounded by a protective wall. The agent is provided with 0.1 to 90% of a pharmaceutically acceptable carrier. A compsn. including a hydrophilic polymer is provided for expanding and pushing the agent from the first wall section such as to exit through an orifice in that section.

USE - For enzyme or hormone dispensing.
Dwg.0/11

ABEQ US 5630808 A UPAB: 19970626
A dispenser for delivering a beneficial agent formulation to a fluid environment of an **animal**, and for protecting the beneficial agent from the fluid environment of the **animal**, the dispenser comprising: (a) a wall that surrounds an internal lumen, which wall comprises: (1) a first section that surrounds a first area of the lumen, comprising means impervious to the passage of fluid into the first section, a lead end and a receiving end; (2) a second section that surrounds a second area of the lumen, comprising means pervious to the passage of fluid into the second section, is free of the means impervious to the passage of fluid, a receiving end which forms a tight fit with the receiving end in the first section and a closed rear end to form the wall which surrounds the internal lumen, the wall being continuous; (b) 20 nanograms to 20 grams of a beneficial agent formulation in the first section for protecting the beneficial agent formulation from fluid; (c) a solid composition comprising a member selected from the group consisting of an osmagent and an osmopolymer in the second section; and (d) exit means in the wall that connects the exterior of the dispenser with the lead end of the first section for delivering the beneficial agent formulation from the dispenser to the **animal** over a prolonged period of time.

Dwg.10/11
ABEQ US 5714160 A UPAB: 19980323
Beneficial agent (20) is accommodated within a receptacle (18), in a portion (16) having fluid impermeable walls (12a) and an exit (13) through which the agent (20) can be dispensed into the environment of use. A second portion (17) of the receptacle has walls (12b) which are capable of permeation by fluids in the environment of use, and contains a substance which expands when subjected to those fluids to exert pressure on and move a fluid impermeable dividing member (27) and so effect ejection of the beneficial agent through the exit (13) into the surrounding environment.
USE/ADVANTAGE - Partic. in the long term delivery of a beneficial drug from a device **implanted** in a human or **animal** body. Can be used to obtain accurately controlled rates of drug delivery while maintaining the integrity of the device and protecting the beneficial agent from deterioration prior to delivery to the environment of use.
Dwg.5/11

L128 ANSWER 10 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1989-285232 [39] WPIDS
CR 1990-312220 [41]; 1991-080668 [11]
DNN N1989-217764 DNC C1989-126343
TI Device for delivering drug, e.,g. **somatotropin** to **animal** - having exit in wall through which drug is forced by driving member.
DC B04 C03 P32 P33 P34
IN CORTESE, R; ECKENHOFF, J B; MAGRUDER, J A; PEERY, J R; WRIGHT, J C; MAGRUDER, A J
PA (ALZA) ALZA CORP
CYC 23
PI US 4855141 A 19890808 (198939)* 14p
EP 337613 A 19891018 (198942) EN
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
AU 8930121 A 19890928 (198947)
NO 8901224 A 19891023 (198948)
DK 8901395 A 19890926 (198949)
BR 8901408 A 19891107 (198950)
PT 90074 A 19891110 (198950)
FI 8901430 A 19890926 (199002)
ZA 8901892 A 19891129 (199002)
JP 01299568 A 19891204 (199003)
EP 337613 B1 19930728 (199330) EN 18p A61M031-00
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
DE 68907769 E 19930902 (199336) A61M031-00
ES 2041988 T3 19931201 (199401) A61M031-00
NO 177887 B 19950904 (199541) A61K009-00
CA 1337038 C 19950919 (199544) A61D007-00
ADT US 4855141 A US 1988-173209 19880325; EP 337613 A EP 1989-302699 19890320; ZA 8901892 A ZA 1989-1892 19890313; JP 01299568 A JP 1989-73734 19890324; EP 337613 B1 EP 1989-302699 19890320; DE 68907769 E DE 1989-607769 19890320, EP 1989-302699 19890320; ES 2041988 T3 EP 1989-302699 19890320; NO 177887 B NO 1989-1224 19890321; CA 1337038 C CA 1989-593490 19890313
FDT DE 68907769 E Based on EP 337613; ES 2041988 T3 Based on EP 337613; NO 177887 B Previous Publ. NO 8901224
PRAI US 1988-173209 19880325
REP EP 40457; GB 2140687; GB 2179252
IC A61D007-00; **A61F002-00**; A61J003-08; A61K009-22; A61M031-00; A61M037-00
ICM A61D007-00; A61M031-00
ICS **A61F002-00**; A61J003-08; A61K009-20; A61K009-22; A61K009-32; A61K009-38; A61M037-00
AB US 4855141 A UPAB: 19951026
A device for delivering a beneficial agent to an **animal** comprises (a) a wall, (b) an internal lumen defined by the wall, (c) an exit in the wall for connecting the exterior with the interior of the device, (d) a beneficial agent compsn. in the lumen comprising a **somatotropin** and a carrier, such that the space occupied by the

beneficial agent compsn. can be reduced and it can be delivered to the **animal**.

The beneficial agent compsn. may comprise **somatotropin** and a cpd. selected from 1,5-pentylene glycol, 1,6-hexylene glycol, 1,7-heptylene glycol, 1,9-nonylene glycol, 1,2-dimethyl-1,6-hexylene glycol, 1,2,3-propanetriol, 1,2,5-pentanetriol, 1,3,5-pentanetriol, 1,2,4-butanetriol and dipentaerythritol. The device can be used for dispensing beneficial agents other than **somatotropin**.

ADVANTAGE - The device can deliver precise release rates over a prolonged period of time while simultaneously maintaining the integrity of the device.

Dwg.0/7

Dwg.0/7

FS CPI GMPI

FA AB; DCN

MC CPI: B04-B02D4; B11-C04; B12-L09; C04-B02D4; C11-C04; C12-L09

ABEQ EP 337613 B UPAB: 19931118

A device for delivering a beneficial agent to an aqueous environement of use wherein said device comprises:- a wall which surrounds and forms a lumen, the wall being, at least in part, permeable or semi-permeable to aqueous fluid; a beneficial agent contained in a first portion of the lumen; an expandable driving member contained in a second portion of the lumen, said member including means for developing an osmotic potential across said wall when said device is in an aqueous environment of use; and exit means; the arrangement being such that in an aqueous environment of use fluid is caused or allowed to enter into the said lumen by osmosis, which fluid causes said member to expand thereby to urge the beneficial agent towards the exit means for delivery therethrough to the environment of use; characterised by impermeable protecting means juxtaposed the said first portion of the lumen thereby to prevent the passage of aqueous fluid in the environment of use across the wall directly into the said first portion of the lumen.

Dwg.0/7

L128 ANSWER 11 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD

AN 1989-033726 [05] WPIDS

DNC C1989-014640

TI Delivery system with barrier coating - retards initial high release from biodegradable polymer matrix.

DC A26 A96 B07 C03 P32

IN KITCHELL, J P; MOREAU, J; MOREAU, J P

PA (BIOM-N) BIOMEASURE INC

CYC 16

PI	EP 301856	A	19890201 (198905)*	EN	4p	
	R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
	WO 8900839	A	19890209 (198908)	EN		
	W: JP					
	US 4894231	A	19900116 (199010)		3p	
	JP 02500521	W	19900222 (199014)			
	CA 1332356	C	19941011 (199441)			A61K009-30
	EP 301856	B1	19950524 (199525)	EN	11p	A61K009-30
	R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
	DE 3853853	G	19950629 (199531)			A61K009-30
	ES 2074050	T3	19950901 (199541)			A61K009-30
	JP 2714415	B2	19980216 (199812)		3p	A61K009-00

ADT EP 301856 A EP 1988-306958 19880728; WO 8900839 A WO 1988-US2546 19880727; US 4894231 A US 1987-78534 19870728; JP 02500521 W JP 1988-507102 19880727; CA 1332356 C CA 1988-573269 19880728; EP 301856 B1 EP 1988-306958 19880728; DE 3853853 G DE 1988-3853853 19880728, EP 1988-306958 19880728; ES 2074050 T3 EP 1988-306958 19880728; JP 2714415 B2 JP 1988-507102 19880727, WO 1988-US2546 19880727

FDT DE 3853853 G Based on EP 301856; ES 2074050 T3 Based on EP 301856; JP 2714415 B2 Previous Publ. JP 02500521, Based on WO 8900839

PRAI US 1987-78534 19870728

REP A3...9030; DE 2824112; EP 206890; EP 263083; No-SR.Pub; US 3854480; US 4351337; US 4622244; WO 8704070; US 3279996; US 3944064; US 4159322; US

4230686
IC **A61F002-00**; A61K009-30; A61K047-34
ICM A61K009-00; A61K009-30
ICS **A61F002-00**; A61K009-22; A61K009-52; A61K047-34; A61K047-44
AB EP 301856 A UPAB: 19930923
Appts. for delivery of an agent (I) to humans or **animals** comprises (I) and a biodegradable polymer and is coated with a barrier substance effective to decrease the amt. of (I) released from the system, c.f. uncoated system, in a period of 48 hrs. immediately following parenteral injection or **implantation**.

The barrier substance is a silicone oil, pref. of viscosity 100-10,000, esp. 500-2000 cP, e.g. Union Carbide dimethylpolysiloxane L-45.

(I) may be a therapeutic agent, fragment or analogue (e.g. **testosterone**, LHRH), diuretic (chlorothiazide), antiinflammatory, pain-killer (morphine), antibiotic (tetracycline), antipsychotic drug, anticancer agent (methotrexate, actinomycin D, vinblastine, cytosine arabinoside), vaccine, or antiarthritic drug (ibuprofen, flurbiprofen). (I) may also be an agent used for **animals** grown for their milk, meat, wool or leather, other than for therapy or diagnosis.

ADVANTAGE - Initial release is retarded so that side effects of high concns. of (I) may be minimised. The coating also reduces clamping of the powder.

0/0
FS CPI GMPI
FA AB; DCN
MC CPI: A06-A00E3; A09-A; A12-V01; B01-C05; B02-Z; B04-A04; B04-B02D1; B04-B02D4; B04-B03A; B04-B04A; B04-C02; B04-C03C; B04-C03D; B06-D09; B06-F02; B10-C04C; B12-C10; B12-D01; B12-D03; B12-D07; B12-G03; B12-G07; C01-C05; C02-Z; C04-A04; C04-B02D1; C04-B02D4; C04-B03A; C04-B04A; C04-C02; C04-C03C; C04-C03D; C06-D09; C06-F02; C10-C04C; C12-C10; C12-D01; C12-D03; C12-D07; C12-G03; C12-G07
ABEQ US 4894231 A UPAB: 19930923
Therapeutic agent delivery system comprises a biodegradable polymer and therapeutic agent, and is coated with a barrier substance that decreases amt. of agent released from syst. w.r.t. one not coated, during 48 hrs. after parenteral injection or **implantation** into living person or **animal**. Barrier substance comprises a paraffin, beeswax or silicone oil and can dissipate from syst. shortly after injection/ **implantation**. Silicone oil has viscosity 100-10,000 centipoise.

ADVANTAGE - Is easy to use and inexpensive to make, with superior handling so that it does not clump together when in powdered form.
ABEQ EP 301856 B UPAB: 19950630
A delivery system adapted for delivery of an agent, such as a therapeutic agent, or other substance to a living person or **animal** by parenteral injection or **implantation**, comprising a biodegradable polymer and a therapeutic agent dispersed in said polymer, and being coated with a barrier substance that is effective, during a period of forty-eight hours immediately subsequent to parenteral injection or **implantation** of said system into a living person or **animal** , to decrease the quantity of said agent or substance released from said system, as compared with the quantity of said agent or substance released from a similar said system not so coated, during said period, said barrier substance being not susceptible to enzymatic attack and one which dissipates in said living person or **animal** substantially by wearing off from the surface of said delivery system.
Dwg.0/0

L128 ANSWER 12 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1988-243279 [35] WPIDS
DNC C1988-108766
TI Sustained-release **implants** - comprising multiple units contg. different **lactide-glycolide** copolymers.
DC A96 B07 C03
IN DEASY, P B
PA (FARH) HOECHST AG

CYC 18
PI DE 3710175 A 19880825 (198835)* 5p
EP 281778 A 19880914 (198837) DE
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
JP 63203610 A 19880823 (198839)
AU 8811641 A 19880818 (198840)
DK 8800705 A 19880813 (198844)
ZA 8800962 A 19880810 (198845)
US 4874612 A 19891017 (198951) 5p
ADT DE 3710175 A DE 1987-3710175 19870327; EP 281778 A EP 1988-101927 19880210; JP 63203610 A JP 1988-27798 19880210; ZA 8800962 A ZA 1988-962 19880211; US 4874612 A US 1988-152004 19880203
PRAI DE 1987-3704275 19870212; DE 1987-3710175 19870327
REP EP 171907; EP 25698; EP 58481; WO 8203174
IC A61K009-00
AB DE 3710175 A UPAB: 19930923
Implants giving sustained release of an active ingredient (I) comprises at least two (I)-contg. solid units, each contg. a biodegradable copolymer of lactic and glycolic acid with a **lactide**: **glycolide** wt. ratio of 90:10 to 60:40. At least one of the units is of type A and at least one of type B, where the copolymer in type A has a glycolide content which is 5-15 wt.% lower than that of the copolymer in type B.
USE/ADVANTAGE - The **implants** may be used in human or **veterinary** medicines, esp. for sustained release of natural or synthetic hormones in **animals**. The combination of different types of unit permits optimum control of release rate over a long period (up to 12 months) without an initial 'burst' effect.
0/0
FS CPI
FA AB; DCN
MC CPI: A05-E02; A12-V; A12-V01; **A12-V02**; B04-C03D; B11-C04A; **B12-M10A**; C04-C03D; C11-C04A; **C12-M10A**
ABEQ US 4874612 A UPAB: 19930923
A multicomponent long-acting **implant** contains at least 2 shaped pieces contg. active cpd. composed of biodegradable copolymers of lactic and glycolic acids in wt. ratio **lactide** : **glycolide** 90:10-60:40, with at least 2 types of shaped pieces A and B. Type A has copolymers with lactide content 5-15 % wt. less than B.
Implant may have up to 20 pieces, pref. an odd number (5-15)(2-7), which may be arranged as chain with a type A piece at both ends, and opt. some pieces without active cpd., or as alternating sequence. Active content is 20-80 % wt., pref. 5-15 % wt. lower in type A than B. Mean MWt of copolymers is 10000-20000 and polydispersivity 1.5-2.5. Each shaped piece may be cylinder 2-6 mm thickness and total length of **implant** 1-4 cm.
USE - Human and vetinary admin. hormones, cancer drugs, birth control, treatment of infections, circulation disorders, mental handicap, parasites, giving steady or increasing release over 4-12 months.

L128 ANSWER 13 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1988-057672 [09] WPIDS
DNC C1988-025650
TI Biodegradable oestradiol **implant** - from poly lactide co-glycolide and solvent washed to give even rate of oestradiol release.
DC A96 B01 C03 P32 P34
IN SCHAAF, M; SCHAAF, M Y C
PA (AMCY) AMERICAN CYANAMID CO
CYC 17
PI EP 257369 A 19880302 (198809)* EN 10p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
AU 8776724 A 19880218 (198815)
ZA 8705897 A 19880328 (198825)
US 4758435 A 19880719 (198831) 5p
CA 1297020 C 19920310 (199216)
EP 257369 B 19920415 (199216) EN 9p

R: AT BE CH DE ES FR GB GR IT LU NL SE
DE 3778244 G 19920521 (199222) A61K009-22
ES 2031096 T3 19921201 (199301) A61K009-22
ADT EP 257369 A EP 1987-111218 19870804; ZA 8705897 A ZA 1987-5897 19870810; US 4758435 A US 1986-895415 19860811; EP 257369 B EP 1987-111218 19870804; DE 3778244 G DE 1987-3778244 19870804, EP 1987-111218 19870804; ES 2031096 T3 EP 1987-111218 19870804
FDT DE 3778244 G Based on EP 257369; ES 2031096 T3 Based on EP 257369
PRAI US 1986-895415 19860811
REP EP 122709; EP 171907; EP 25698; FR 2070153
IC ICM A61K009-22
ICS A61D000-00; A61K031-56; A61K031-565; A61K047-00; A61L027-00; A61M007-00
AB EP 257369 A UPAB: 19930923
Biodegradable **implant** comprises 65 to 80 percent by wt oestradiol and 20 to 35 percent by wt poly (lactide-co-glycolide) polymer with a **lactide-glycolide** ratio from 75/25 to 95/5.
Pref. the **implant** is washed with a solvent after mfr to give an oestradiol-free external layer and then coated with oxytetracycline HCl.
USE/ADVANTAGE - The **implant** is used in **ruminants** to increase weight gain. It is biodegradable and gives a release of (I) over a long period at a rate of 25 to 35 microgram/day for 110 to 200 days. The solvent washing creates fine pores in the surface of the **implant** which improve the release characteristics.
0/0
FS CPI GMPI
FA AB; DCN
MC CPI: A05-E02; A12-V; A12-V01; A12-W04; B01-A02; B04-C03D; B11-C04A; B12-L09; **B12-M10A**; C01-A02; C04-C03D; C11-C04A; C12-L09; **C12-M10A**
ABEQ DE 3778244 G UPAB: 19930923
Biodegradable **implant** comprises 65 to 80 percent by wt oestradiol and 20 to 35 percent by wt poly (lactide-co-glycolide) polymer with a **lactide-glycolide** ratio from 75/25 to 95/5.
Pref. the **implant** is washed with a solvent after mfr to give an oestradiol-free external layer and then coated with oxytetracycline HCl.
USE/ADVANTAGE - The **implant** is used in **ruminants** to increase weight gain. It is biodegradable and gives a release of (I) over a long period at a rate of 25 to 35 microgram/day for 110 to 200 days. The solvent washing creates fine pores in the surface of the **implant** which improve the release characteristics.
ABEQ EP 257369 B UPAB: 19930923
A biodegradable **implant** composition comprising on a weight basis 65% to 80% **estradiol** and 20% to 35% of a poly(lactide-co--glycolide) polymer having a **lactide/glycolide** ratio in the range of from 72/25 to 95/5, which has been washed with a solvent in which **estradiol** is freely soluble to provide a porous **estradiol** free coating having an average pore size of less than twenty micrometres. ()
ABEQ US 4758435 A UPAB: 19930923
A biodegradable **implant** compsn. (I) contains 65-80(70-80)wt.% **estradiol** (II) and 20-35(20-30)wt.% of a poly(lactide-co-glycolide) polymer (III) having an L-**lactide/glycolide** ratio of 75125-95/5 (80/20-95/5).
(III) has been washed with an alcohol, a ketone or an ether to give a porous **estradiol** free coating having a pore size less than 20 micrometres.
USE/ADVANTAGE - (I) is given parenterally to **animals** and gives a continuous prolonged release of (II), which is used to increase weight gain.

L128 ANSWER 14 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1980-03542C [02] WPIDS
TI **Implant** for **animals** esp. **ruminants** to

promote growth - with inert core coated with **estradiol** or its benzoate and polyethylene glycol.
DC A96 B05 C03
IN KATZ, M; KENT, J S
PA (SYNT) SYNTEX CORP
CYC 1
PI US 4180560 A 19791225 (198002)*
PRAI US 1975-572031 19750428; US 1976-735727 19761026; US 1978-903284 19780505
IC A61K009-22
AB US 4180560 A UPAB: 19930902
Solid spherical pellet comprises (a) a biocompatible inert spherical core of diameter 2-10 mm and (b) >=1 biocompatible and biosoluble coating of uniform thickness 0.05-10 mm adhering to the core and covering it completely. The coating comprises 5-90% **estradiol** and/or its benzoate, and 10-95% polyethylene glycol of molecular wt. 3000-20000 as sole carrier. The core is >= one-half the diameter of the total pellet.
The pellet is **implanted** in **animals**, esp **ruminants**, to give constant release of the drug over a given time, with an abrupt termination of that release without removal of the pellet. The **animal** shows a greater than normal wt. gain. The pellet is easily prepd and a redn. of total administered dose of the drug is possible. the pellet is easily **implanted** with a simple injection device and without surgery. Similar pellets on which other coatings may be present are described in 60413A/33.
FS CPI
FA AB
MC CPI: A05-H03; A12-V; A12-V01; A12-W05; B01-A02; B04-C02; B04-C03C; B04-D01; B11-C04A; **B12-M10**; B12-M11; C01-A02; C04-C02; C04-C03C; C04-D01; C11-C04A; **C12-M10**; C12-M11

L128 ANSWER 15 OF 15 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1978-60413A [33] WPIDS
TI **Implant** for **ruminants** to promote growth - with inert core coated with **estradiol** or its benzoate.
DC A25 A96 B04 C03
IN KATZ, M; KENT, J S
PA (SYNT) SYNTEX CORP
CYC 1
PI US 4096239 A 19780620 (197833)*
PRAI US 1975-572031 19750428; US 1976-735727 19761026; US 1978-903284 19780505
IC A61K009-22; A61K031-56
AB US 4096239 A UPAB: 19930901
Solid, spherical pellet comprises (a) a biocompatible inert spherical core of diameter 2-10 mm. and (b) >=1 coating of uniform thickness 0.05-10 mm. adhering to the core and covering it completely. The coating comprises 5-90% **estradiol** and/or its benzoate and 10-95% carrier. The core is >= one-half the diameter of the total pellet.
For **implantation** in a **ruminant** to produce a constant release of active agent over a given time, with an abrupt termination of that release; the **ruminant** shows a greater than normal wt. gain. The pellet is easily prepd. and a redn. in the total drug dose may be achieved over the normal dose. The pellet is **implanted** with a simple injection device.
In an example **cellulose** acetate spheres were coated with **estradiol benzoate**, cholesterol and polyethylene glycol 6000 in CHCl3-i-PrOH.
FS CPI
FA AB
MC CPI: A12-V01; B01-A02; B01-D02; B04-C02; B04-C03C; B12-L09; **B12-M10**; B12-M11; C01-A02; C01-D02; C04-C02; C04-C03C; C12-L09; **C12-M10**; C12-M11

=> d all abeq tech tot l129

L129 ANSWER 1 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-237788 [20] WPIDS
DNN N2000-178295 DNC C2000-072448
TI Drug delivery device for a stent comprises a biocompatible polymer sheath for mounting on the stent and containing drugs to be delivered to the site.
DC A96 B07 D22 P32 P34
IN WANG, L; YANG, D
PA (SCIM-N) SCIMED LIFE SYSTEMS INC
CYC 20
PI WO 2000012147 A1 20000309 (200020)* EN 27p A61L031-08
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP
ADT WO 2000012147 A1 WO 1999-US19697 19990831
PRAI US 1998-145707 19980902
IC ICM A61L031-08
ICS **A61F002-06**; A61K051-12; A61L031-16; A61L031-18
AB WO 200012147 A UPAB: 20000426
NOVELTY - An **implantable** intraluminal apparatus comprises an expandable intraluminal stent comprising a main body with a flow passage through it, and a sheath, comprising a biocompatible polymer carrying a drug, constructed and arranged for mounting on the stent to deliver the drug.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) an **implantable** intraluminal apparatus comprising a sheath comprising a biocompatible polymeric material and a carried drug, for mounting on a stent to deliver drugs;

(2) a sheath constructed for mounting on a stent, comprising a biocompatible polymeric material and a carried drug;

(3) a sheath for an **implantable** intraluminal apparatus for delivery of a stent, the sheath constructed and arranged for mounting on a stent and comprising a biocompatible polymeric material and a carried drug;

(4) a sheath for delivery into the body with a stent, for drug delivery, the sheath comprising a biocompatible polymeric material and a carried drug;

(5) a drug delivery sheath for delivering drugs in the body, comprising a biocompatible polymeric material and a carried drug, arranged to associated with a stent; and

(6) a sheath constructed and arranged for being introduced into the body for drug delivery, comprising a biocompatible polymeric material and a carried drug.

ACTIVITY - Vasotropic.

MECHANISM OF ACTION - None given.

USE - The apparatus provides mechanical support to a vessel lumen and delivers materials which prevent restenosis.

ADVANTAGE - The device may be biodegradable, which allows the controlled release of a drug into the vessel lumen as the device degrades. The device can be used with existing stents, providing a simple method for reducing restenosis.

Dwg.0/11
FS CPI GMPI
FA AB; DCN
MC CPI: A09-A; **A12-V02**; B04-C02A; B04-C03B; B11-C04; D09-C01
TECH UPTX: 20000426
TECHNOLOGY FOCUS - POLYMERS - Preferred Composition: The sheath or its coating, preferably comprises polyurethane, polytetrafluoroethylene, a gel-like material, **cellulose** polymer, a biodegradable polymer, poly(N-vinyl-2-pyrrolidone) or polyethylene oxide. The drug is preferably a pharmaceutical agent, radioactive agent and/or bioactive agent, especially taxol, vascular endothelial growth factor (VEGF), heparin, 5-fluorouracil, beta-**estradiol**, tranilast, trapidil, probucol or angiopeptin. The sheath may be covered by a coating, preferably a

biocompatible polymer, especially polyethylene oxide or polyurethane, and may include a bioadhesive, preferably cyanoacrylate, fibrin glue or gelatin-resorcinol-formol glue.

TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred apparatus: The sheath is cylindrical, and preferably includes a helical longitudinal slit so that the sheath is a helical coil and may comprise a number of layers. The sheath comprises more than one layer of the same or different material, at least one of which is a drug. The stent is 1-50mm in diameter and length. The tubular main body can have a length upto 5cm.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: The drugs which are delivered can be thrombolytics, antiproliferatives, antioxidants, lymphokines, growth factors, prostaglandins or leukotrienes. The sheath may also contain bioactive molecules such as fibronectin, laminin, elastin, collagen or intergrins.

L129 ANSWER 2 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 2000-195164 [17] WPIDS
DNC C2000-060465
TI Moldable solid **implant** composition for sustained delivery of an active agent comprising a thermoplastic polymer, organic solvent and small amount of aqueous medium.
DC A96 B07 D22
IN CHANDRASHEKAR, B L; DUNN, R L; MCENERY, K A
PA (ATRI-N) ATRIX LAB INC
CYC 85
PI WO 2000006117 A1 20000210 (200017)* EN 24p A61K009-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
ADT WO 2000006117 A1 WO 1999-US15519 19990708
PRAI US 1998-123723 19980728
IC ICM A61K009-00
AB WO 200006117 A UPAB: 20000405
NOVELTY - An **implant** composition for sustained delivery of an active agent comprising active agent, a thermoplastic polymer, organic solvent and small amount of aqueous medium, is moldable for adaptation to an **implant** site, but then becomes hard and rigid.
DETAILED DESCRIPTION - A pliable, moldable, **implant** composition for sustained delivery of an active agent comprises a biocompatible, biodegradable, water-insoluble thermoplastic polymer combined with an active agent, organic solvent and an amount of an aqueous medium just sufficient to cause some of the thermoplastic polymer to precipitate or coagulate.
USE - For sustained release delivery of an active agent, e.g. antibacterial, antiviral or antiinflammatory agents, local anesthetics, growth promoters, antiparasitics, analgesics, vaccines, osteoinductives, antineoplastics, hormones, antihistamines, cardiovascular agents, antiulcer agents, bronchodilators, vasodilators, central nervous system agents, antipsychotics, narcotic antagonists and genes encoding biologically useful proteins.
No example demonstrating this use is given.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: A12-V; A12-V01; B01-B01; B01-C01; B01-C04; B02-V; B04-A01; B04-A04; B04-C01B; B04-C01F; B04-H01; B04-H05; B04-J03A; B04-L02; B05-A03B; B06-D02; B06-D06; B06-D09; B06-D11; B06-F02; B06-F05; B07-A02B; B07-A03; B07-D04C; B07-D05; B07-D08; B07-D12; B10-A22; B10-B03A; B10-B04A; B10-C03; B10-C04C; D09-C01
TECH UPTX: 20000405
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The organic

solvent may have high water solubility, and may be a combination of solvents with high and low water solubilities.
The thermoplastic polymer incorporates monomeric units such as **lactides**, **glycolides**, caprolactones, glycerides, anhydrides, amides, urethanes, esteramides, orthoesters, dioxanones, acetals, ketals, carbonates, phosphazenes, hydroxybutyrates, hydroxyvalerates, alkylene oxalates, alkylene succinates, and amino acids, and the formula contains the monomeric units in random or block order. A preferred polymer is a copolymer of 2 or more lactide, caprolactone or glycolide monomeric units.
The composition comprises 5-40 vol.% aqueous medium relative to the volume of a flowable composition of the thermoplastic polymer and the organic solvent.

L129 ANSWER 3 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-105498 [09] WPIDS
DNN N1999-076200 DNC C1999-031342
TI Expandable stent for e.g. blood vessels and urethra - has framework with first polymer layer completely surrounded by outer polymer layer and layers have different time periods of biodegradation.
DC A96 B07 D22 P32
IN WANG, L; YANG, D
PA (SCIM-N) SCIMED LIFE SYSTEMS INC
CYC 20
PI WO 9856312 A1 19981217 (199909)* EN 20p A61F002-06 <--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP
ADT WO 9856312 A1 WO 1998-US12228 19980611
PRAI US 1997-874190 19970613
IC ICM **A61F002-06**
AB WO 9856312 A UPAB: 19990302
Stent has a framework with apertures distributed about it. The framework has a first polymer layer completely surrounded by an outer polymer layer. The layers have different time periods of biodegradation. The outer layer may be of polyamide, polyorthoester, or polyanhydride and gel-like. The first layer may be of poly(D,L-lactide), poly(L-**lactide**), **polyglycolide** or polystyrene oxide, polydioxanone, polycaprolactone, polyhydroxybutyrate, polyphophazene or poly(phosphate ester) or block copolymers of some of these. The first layer may include the drugs, e.g. p21, VEGF, Taxol and/or Beta-**Estradiol**.
USE - An expandable stent for e.g. blood vessels, urethra is provided. The stent may deliver a drug preventing restenosis
ADVANTAGE - The stent is flexible and compliant and has sufficient hoop strength to support the vessel wall.
Dwg.9/9
FS CPI GMPI
FA AB; GI; DCN
MC CPI: A12-V02; B11-C04A; B11-C04B; B11-C09; D09-C01B

L129 ANSWER 4 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1995-373616 [48] WPIDS
DNC C1995-161869
TI Controlled active agent, e.g. drug, delivery system - utilising chemical oscillating reaction, pref. giving oscillating pH, to activate delivery esp. in transdermal device.
DC A96 B07 C07
IN BERNER, B; GIANNOS, S A; MINH, DINH S
PA (CIBA) CIBA GEIGY AG; (NOVS) NOVARTIS AG
CYC 65
PI WO 9528144 A1 19951026 (199548)* EN 66p A61K009-00
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AU BB BG BR BY CA CN CZ EE FI GE HU IS JP KG KP KR KZ LK LR LT LV MD MG MN MX NO NZ PL RO RU SG SI SK TJ TM TT UA US UZ VN
AU 9519582 A 19951110 (199607) A61K009-00
EP 755244 A1 19970129 (199710) EN A61K009-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

JP 09512006 W 19971202 (199807) 67p A61K009-00
AU 9918467 A 19990506 (199929) A61K009-00
ADT WO 9528144 A1 WO 1995-IB223 19950403; AU 9519582 A AU 1995-19582 19950403; EP 755244 A1 EP 1995-912380 19950403, WO 1995-IB223 19950403; JP 09512006 W JP 1995-526829 19950403, WO 1995-IB223 19950403; AU 9918467 A Div ex AU 1995-19582 19950403, AU 1999-18467 19990226
FDT AU 9519582 A Based on WO 9528144; EP 755244 A1 Based on WO 9528144; JP 09512006 W Based on WO 9528144
PRAI US 1994-226917 19940413
REP 2.Jnl.Ref; WO 9202464
IC A61K009-70
ICM A61K009-00
ICS A01N025-00; A01N025-26; A61K009-20; A61K009-48; A61K009-70
AB WO 9528144 A UPAB: 19970612
A method of using a chemical oscillating reaction (OR) comprises activating the OR within an active agent (A) delivery system which is sensitive to at least one reactant or product of OR. The initial oscillation frequency corresponds to an oscillation period of not less than 1.5 times the period necessary for delivery of (A) under the OR conditions permitting delivery. The delivery occurs passively once OR is activated. Also claimed is an (A) delivery device, for passive temporal or periodic control of delivery, comprising: (a) (A), or a precursor modified in situ into (A); (b) some or all of the initial reactants of an OR, such that OR is not initiated until desired; and (c) a separator for at least one of the reactants from the remaining reactants before OR activation (if all the reactants are contained in the device before activation) or an introduction device for any reactants not present before activation. OR is activated by contacting all of the initial reactants or by subjecting the reactants to activating conditions. Delivery of (A) is passively controlled in response to the oscillations of OR.

USE - (A) is specifically a pharmaceutical, cosmetic or agricultural active agent. The system is e.g. a transdermal drug delivery system, infusion pump or **implant**, esp. a user-activated transdermal therapeutic system.

ADVANTAGE - The OR components may be stabilised during storage and activated when desired. The release may be controlled to provide improved efficacy, avoid or minimise tolerance of (A) or synchronise with rhythmic body cycles (esp. in treatment of diseases associated with circadian rhythm disorders.

Dwg.17/17
FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; A12-V03; B11-C04; C11-C04; B12-M02F; C12-M02F

L129 ANSWER 5 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-176586 [22] WPIDS
DNN N1992-133228 DNC C1992-080923
TI Controlled release microparticles contg. polysaccharide gelling agent etc. - comprise biodegradable polymer, interfacial agent, amphiphilic polymer and active substance esp. calcitonin etc..
DC A11 A96 B07
IN CANAL, T; CARLI, F; LOURECICH, M L; LOVRECICH, M L
PA (VECT-N) VECTORPHARMA INT SPA
CYC 16
PI EP 486959 A1 19920527 (199222)* EN 19p A61K009-16
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
JP 04283510 A 19921008 (199247) 14p A61K009-14
IT 1243390 B 19940610 (199441) A61K000-00
US 5536508 A 19960716 (199634) 10p A61K009-50
EP 486959 B1 19960828 (199639) EN 16p A61K009-16
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69121675 E 19961002 (199645) A61K009-16
ES 2094781 T3 19970201 (199712) A61K009-16
US 5700486 A 19971223 (199806) A61K009-50
ADT EP 486959 A1 EP 1991-119505 19911115; JP 04283510 A JP 1991-332735 19911122; IT 1243390 B IT 1990-22155 19901122; US 5536508 A Cont of US

1991-794905 19911120, US 1993-139051 19931021; EP 486959 B1 EP 1991-119505 19911115; DE 69121675 E DE 1991-621675 19911115, EP 1991-119505 19911115; ES 2094781 T3 EP 1991-119505 19911115; US 5700486 A Cont of US 1991-794905 19911120, Div ex US 1993-139051 19931021, US 1996-641039 19960430

FDT DE 69121675 E Based on EP 486959; ES 2094781 T3 Based on EP 486959; US 5700486 A Div ex US 5536508

PRAI IT 1990-22155 19901122

REP 1.Jnl.Ref; DE 3916020; EP 269921; EP 274961; FR 2620621; GB 2077693; JP 62059207; US 4568559; US 4622244

IC ICM A61K000-00; A61K009-14; A61K009-16; A61K009-50
ICS **A61F002-02**; A61K037-30; A61K037-36; A61K037-43; A61K047-30; A61K047-32; B01J013-02

AB EP 486959 A UPAB: 19931006
Pharmaceutical compsns. in the form of particles dia. 0.1-150 microns, suitable for controlled release of active substances, comprise: (a) a biodegradable polymer and/or a polysaccharide jellifying and/or bioadhesive polymer; (b) an amphiphilic polymer; (c) an agent modifying the interface properties; and (d) an active substance.

The biodegradable polymer is polylactic or polyglycolic acid or their copolymers, polyhydroxybutyric acid, polycaprolactone, a polyorthoester, polyanhydride, chitin, chitosan, hyaluronic acid, collagen or copolymers. The polysaccharide polymer is scleroglucan, xanthan, chitin and chitosans, **cellulose** or an alginate. The amphiphilic polymer (b) is a polyethylene glycol, PVP or PVA. Agents modifying the interface properties (c) are sorbitan esters, polysorbates, lecithus, stearic acid or stearate. The active substance (d) is a CNS active medicament, cardiovascular, hypotensive, diuretic, antiphlogistic, analgesic, antipyretic, anti-asthma, protein, polypeptide, vaccine esp. calciotonic, LH-RH analogue, somatostatin, **somatotropin**, broxaterol or its hydrochloride, nicergoline, megesterol acetate, adriamycin or levonorgestrel.

USE/ADVANTAGE - The use of solvents can be avoided by dissolving (a) and (c) directly in (b). The prods. also have improved biocompatibility.
0/0

FS CPI

FA AB; DCN

MC CPI: A12-V01; B01-C05; B01-C06; B02-V02; B02-Z; B04-B01B; B04-B02D; B04-B04A6; B04-C01; B04-C02; B04-C03; B05-B01P; B06-D18; B07-A02; B07-E01; B10-C04E; B12-A01; B12-A06; B12-D01; B12-D02; B12-D07; B12-D08; B12-F01C; B12-F05; B12-G03; B12-G04; B12-G07; B12-K01; B12-K02; B12-K06; B12-M10A

ABEQ US 5536508 A UPAB: 19960829
A pharmaceutical composition, in the form of particles having a diameter from 0.1 to 150 mum, suitable for the controlled release of a pharmaceutically active substance, comprising a biodegradable polymer, an amphiphilic polymer, an agent modifying the interface properties at a concentration between 0.1 and 99.9%, and a therapeutically effective amount of the pharmaceutically active substance at a concentration between 0.01 and 99.9% for those in need thereof, wherein said particles have separate intraparticle polymeric phases with different thermal characteristics when the content of the amphiphilic polymer is from 30 to 50% by weight relative to the biodegradable polymer.
Dwg.0/0

ABEQ EP 486959 B UPAB: 19961004
Pharmaceutical compositions, in the form of particles having a diameter from 0.1 and 150 micron m, suitable for the controlled release of the active substance, comprising a biodegradable polymer consisting of co-poly (**lactic-glycolic**) acid, an amphiphilic polymer consisting of polyethyleneglycol (PEG 400), an agent modifying the interface properties and an active substance, characterized in that the said particles have separate phases with different thermal characteristics when the content of said amphiphilic polymer is from 30 to 50% by weight relative to said biodegradable polymer.
Dwg.0/0

ABEQ US 5700486 A UPAB: 19980209
Pharmaceutical compositions in the form of particles diameter 0.1-150

microns, suitable for controlled release of active substances, comprise: (a) a biodegradable polymer and/or a polysaccharide jellifying and/or bioadhesive polymer; (b) an amphiphilic polymer; (c) an agent modifying the interface properties; and (d) an active substance.

The biodegradable polymer is polylactic or polyglycolic acid or their copolymers, polyhydroxybutyric acid, polycaprolactone, a polyorthoester, polyanhydride, chitin, chitosan, hyaluronic acid, collagen or copolymers. The polysaccharide polymer is scleroglucan, xanthan, chitin and chitosans, **cellulose** or an alginate. The amphiphilic polymer (b) is a polyethylene glycol, PVP or PVA. Agents modifying the interface properties (c) are sorbitan esters, polysorbates, lecithus, stearic acid or stearate. The active substance (d) is a CNS active medicament, cardiovascular, hypotensive, diuretic, antiphlogistic, analgesic, antipyretic, anti-asthma, protein, polypeptide, vaccine especially calciotonic, LH-RH analogue, somatostatic, **somatotropin**, broxaterol or its hydrochloride, nicergoline, megesterol acetate, adriamycin or levonorgestrel.

USE/ADVANTAGE - The use of solvents can be avoided by dissolving (a) and (c) directly in (b). The products also have improved biocompatibility.

L129 ANSWER 6 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1991-324931 [44] WPIDS
DNC C1991-140317
TI Capsules for controlled release of drugs, etc. - which are coated with an osmotic compsn. surrounded by semipermeable membrane.
DC B07 C03 D22 J04 P34
IN BARCLAY, B L; DEALEY, M H; THEEUWES, F; WONG, P; WONG, P S L; WONG, P S
PA (ALZA) ALZA CORP
CYC 25
PI WO 9115196 A 19911017 (199144)* 41p
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE
W: AU FI JP KR NO
CA 2039456 A 19911003 (199151)
AU 9176737 A 19911030 (199205)
PT 97203 A 19911231 (199206)
ZA 9102380 A 19920129 (199209)
FI 9204419 A 19921001 (199302) A61K000-00
EP 523172 A1 19930120 (199303) EN 41p A61K009-22
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
NO 9203756 A 19921202 (199310) A61K000-00
NZ 237642 A 19930727 (199333) A61K009-52
AU 645315 B 19940113 (199408) A61K009-66
US 5324280 A 19940628 (199425) 16p A61K009-22
EP 523172 B1 19950104 (199506) EN 16p A61K009-22
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69106501 E 19950216 (199512) A61K009-22
IE 62394 B 19950125 (199517) A61K009-52
JP 07502252 W 19950309 (199518) 41p A61K009-00
US 5413572 A 19950509 (199524) 15p A61K009-22
ES 2075444 T3 19951001 (199545) A61K009-22
JP 2927956 B2 19990728 (199935) 15p A61K009-00
ADT ZA 9102380 A ZA 1991-2380 19910328; FI 9204419 A WO 1991-US2176 19910328, FI 1992-4419 19921001; EP 523172 A1 EP 1991-908069 19910328, WO 1991-US2176 19910328; NO 9203756 A WO 1991-US2176 19910328, NO 1992-3756 19920928; NZ 237642 A NZ 1991-237642 19910328; AU 645315 B AU 1991-76737 19910328; US 5324280 A US 1990-502705 19900402; EP 523172 B1 EP 1991-908069 19910328, WO 1991-US2176 19910328; DE 69106501 E DE 1991-606501 19910328, EP 1991-908069 19910328, WO 1991-US2176 19910328; IE 62394 B IE 1991-1040 19910328; JP 07502252 W JP 1991-507622 19910328, WO 1991-US2176 19910328; US 5413572 A Cont of US 1990-502705 19900402, US 1994-203135 19940218; ES 2075444 T3 EP 1991-908069 19910328; JP 2927956 B2 JP 1991-507622 19910328, WO 1991-US2176 19910328
FDT EP 523172 A1 Based on WO 9115196; AU 645315 B Previous Publ. AU 9176737, Based on WO 9115196; EP 523172 B1 Based on WO 9115196; DE 69106501 E Based on EP 523172, Based on WO 9115196; JP 07502252 W Based on WO 9115196; US 5413572 A Cont of US 5324280; ES 2075444 T3 Based on EP 523172; JP 2927956

B2 Previous Publ. JP 07502252, Based on WO 9115196
PRAI US 1990-502705 19900402; US 1994-203135 19940218
REP GB 2182559; US 3995631
IC ICM A61K009-22; A61K009-52; A61K009-66
ICS A61K009-58; A61K009-62; A61L015-44; A61M031-00; A61M037-00
AB WO 9115196 A UPAB: 19930928
Capsules for controlled release of a beneficial agent (I) into a fluid environment contain a liq. formulation of (I), are coated with an osmagent compsn. (II) surrounded by a semipermeable membrane (III), and have at least one opening communicating with the exterior.

Pref. (I) is a Ca antagonist or ACE inhibitor. The formulation of (I) also contains carriers (esp. opt. modified glycerides), surfactants and/or antioxidants. (II) is an osmotically effective solute, e.g. a salt or carbohydrate, or a hydrogel-forming polymer. (III) is permeable to fluid from the environment but impermeable to the formulation of (I).

USE/ADVANTAGE - The capsules may be used to release drugs, biocides, antioxidants, air purifiers, catalysts, chemical reactants, disinfectants, agricultural chemicals, etc.

0/6
FS CPI GMPI
FA AB; DCN
MC CPI: B03-H; B04-B04A6; B04-C02A2; B04-C02A3; B12-F05; B12-G01; **B12-M10A**; B12-M11C; C03-H; C04-B04A6; C04-C02A2; C04-C02A3; C12-F05; C12-G01; **C12-M10A**; C12-M11C; D09-A01; D09-B; D10-A05B; J04-A06
ABEQ US 5324280 A UPAB: 19940810
Osmotic system for delivering a beneficial agent (BA) formulation at a controlled rate to a fluid environment comprises: (a) a gelatin capsule comprising a body and a cap joined to provide an internal lumen; (b) BA in the lumen; (c) an osmagent compsn. on the outside wall of the capsule; (d) a semipermeable compsn. surrounding the osmagent compsn.; and (e) at least one orifice that communicates with the exterior and the lumen for delivering BA from the osmotic system.

The BA is pref. diltiazem, angiotensin converting enzyme inhibitor, a steroid, polypeptide or e.g. lisinopril, captopril, delapril, cimetidine, ranitidine etc.

ADVANTAGE - The system overcomes disadvantages associated with prior art and can be infed into various sizes, shapes and forms. It allows delivery of previously difficult to deliver drugs.

Dwg.2B/6
ABEQ EP 523172 B UPAB: 19950214
An osmotic system (10) for the delivery of a controlled rate of a beneficial agent formulation to a fluid environment of use, the osmotic system comprising: (a) a hard capsule comprising two parts (14a, 14b) assembled telescopically to provide a lumen (15); (b) a liquid formulation comprising a dosage amount of a beneficial agent in the lumen; (c) an osmagent composition (13) on an outside wall (14) of the capsule; (d) a semipermeable composition (12) surrounding the osmagent composition; and (e) at least one orifice (21) that communicates between the lumen and the environment of use for delivering the beneficial agent formulation from the osmotic system to said environment of use; the arrangement being such that, in use, the osmagent composition absorbs fluid from the fluid environment of use by osmosis thereby causing or allowing the osmagent composition to expand and push inwardly against the hard capsule, thereby causing the two capsule parts to move relative to one another so as to diminish the volume of the lumen and increase the pressure of the liquid formulation therein, whereby said liquid formulation is delivered from the lumen through the orifice into the fluid environment of use.

Dwg.1/5
ABEQ US 5413572 A UPAB: 19950626
An osmotic system includes a gelatin capsule with an internal lumen (15) housing a dosage amt. of a liq. (16), a hydro-activated compsn., pref. a hydrogel (13), on the capsule outside wall (14) surrounded by a semipermeable, pref. homopolymer or copolymer, membrane (12) and a passageway (21) connecting the interior and the exterior.

The gelatin has a viscosity of 15-20 mP and the passageway has been

formed by, eroding, extracting, dissolving, bursting or leaching.
USE - Osmotic dosage system for delivering a liq. drug for use in (claimed) buccal, **implant**, anal, cervical, vaginal, subcutaneous, oral and nasal environment or intrauterine, dermal, percutaneous environment. The system is also used for packaging and delivering breath fresheners or bubble baths, bath oils and delivering agents to streams, aquaria, fields, hot houses, farms, zoos, industrial, medical and military environments, etc..
Dwg.2b/6

L129 ANSWER 7 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1991-200619 [27] WPIDS
CR 1989-317658 [44]; 1992-390091 [47]
DNC C1991-086838
TI Drug dosage form for delivery to fluid environment - has annealed coating formed from **cellulosic** sub coat and overcoat layers.
DC B07
IN EDGREN, D E; THEEUWES, F
PA (ALZA) ALZA CORP
CYC 1
PI US 5024842 A 19910618 (199127)*
ADT US 5024842 A US 1990-503004 19900402
PRAI US 1988-187621 19880428; US 1990-503004 19900402
IC A61K009-24
AB US 5024842 A UPAB: 19930928
Dosage form for delivering a drug to a fluid environment comprises (a) a wall comprising an annealed subcoat and overcoat, annealed at 20-75 deg.C for 5-90 hrs., where: (1) the subcoat coprises a fluid-permeable **cellulose** ether, **cellulose** ester or **cellulose** ester-ether and emulsifier(s) which keeps its physical and chemical integrity in fluid; (2) the overcoat comprises HPC, HPMC, CMC or MC, and loses its physical and chemical integrity in fluid; the wall surrounding (b) a compartment; (c) a therapeutically effective amt. of drug in the compartment; and (d) at least one passageway in the wall, connecting the exterior with the interior for delivering the drug over time. The emulsifier in the subcoat may be nonionic, anionic or cationic.
USE/ADVANTAGE - The annealing process removes stresses and strains produced during wall-forming and fabrication, and increases polymer density, heat resistance, high temp. dimensional stability, permeability and impact strength.
The dosage form may be an osmotic delivery system, tablet, capsule, etc. for delivery of a variety of organic and inorganic drugs and medicinal agents, pref. to the gastrointestinal tract but also as **implants** or forms for cervical or intrauterine delivery, etc.
0/8
FS CPI
FA AB; DCN
MC CPI: B04-C02A2; B04-C02A3; B04-C03A; B04-C03C; B05-A01A; B10-C04E; B10-G02; B11-C04A; B12-J01; B12-M11
ABEQ EP 339811 B UPAB: 19930928
A delivery device comprising:- a semi-permeable wall which defines an internal compartment arranged to contain an active agent formulation; and exit means formed in the wall; wherein the wall includes; an annealed subcoat and an overcoat wherein the subcoat comprises a member selected from the group consisting of a **cellulose** ether, a **cellulose** ester and a **cellulose** ester=ether; a plasticizer; and an emulsifier comprising a member selected from the group consisting of nonionic, anionic and cationic emulsifiers; and the overcoat comprises a member selected from the group consisting of **hydroxypropylcellulose**, **hydroxypropylmethylcellulose**, **carboxymethylcellulose** and **methylcellulose**; and a plasticizer; the arrangement being such that fluid in the environment of use permeates through the wall and causes the active agent formulation to be delivered via the exit means.
6/8

L129 ANSWER 8 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1990-356383 [48] WPIDS
DNN N1990-272194 DNC C1990-154813
TI New percutaneous rate controlled delivery system - comprising drug, penetration enhancer and polymeric particles in a matrix layer.
DC A96 B07 D22 P34
IN HELLER, J; KATZ, M; NACHT, S
PA (ADPO-N) ADV POLYMER SYST IN
CYC 15
PI EP 399765 A 19901128 (199048)*
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
JP 03005419 A 19910111 (199108)
US 5028435 A 19910702 (199129)
EP 399765 A3 19920916 (199339)
ADT EP 399765 A EP 1990-305492 19900521; JP 03005419 A JP 1990-130407 19900522; US 5028435 A US 1989-355718 19890522; EP 399765 A3 EP 1990-305492 19900521
PRAI US 1989-355718 19890522
REP NoSR.Pub; EP 227252; EP 306236; EP 328145; US 3598123; US 3797494; US 3996934
IC A61K009-70; A61K013-02; A61L015-24; A61M035-00
AB EP 399765 A UPAB: 19931123
System for percutaneous rate-controlled delivery comprises (a) means for mechanically supporting the matrix layer, (b) drug within the matrix layer, (c) chemical penetration enhancer within the matrix layer, and (d) polymeric particles dispersed in the matrix layer defining a network of internal pores which entrap and release at least one of (c) and (b) into the matrix layer at preselected rates whereby the rate of (c) or (b) release controls the rate at which (b) is systematically absorbed by a host.

USE/ADVANTAGE - Transdermal delivery has the advantage of optimisation of systemic conc., enhanced therapeutic efficacy, reduced frequency of dosage, reduced side-effects and hepatic by-pass which can increase the effectiveness of (b). Isolation of (c) and the matrix layer prevents adverse chemical reactions between them and the slow release rate over an extended period of time minimises adverse effects due to relatively high concns. of (c). The system may be used to treat all types of vertebrate hosts by placing externally on the skin or it may be used internally in the form of **implants**, oral lozenges, suppositories, intrauterine devices, ocular inserts etc. When used externally it may be necessary to periodically rub the backing layer to release (c) (and opt. (b))from the polymeric particles into the matrix layer. The system is useful with practically all drugs esp. those requiring (c) to increase transport of the drug across the skin. @(10pp Dwg.No.1/4)@
1/4
FS CPI GMPI
FA AB; GI
MC CPI: A12-V01; A12-V03A; B04-C03B; B12-C01; B12-C02; B12-D01; B12-F06; B12-M02D; B12-M02F; **B12-M10**; D09-C04
ABEQ US 5028435 A UPAB: 19930928
A drug is released in a controlled manner by a device consisting of (A) a matrix layer, pref. consisting, e.g., of ethene/vinyl acetate copolymer, plasticised PVC, (B) a mechanical support for layer (A), (C) a drug distributed in (A), (D) numerous polymer particles dispersed in (A) defining a network of internal pores entrapping and releasing a chemical penetration enhancer into (A) at a release rate controlling the rate of systematic absorption of the drug from the matrix by a host, and pref. also (E) means to secure (B) to the skin or membrane of the host, pref. an adhesive surface.

The drug can be, e.g., an analgesic, antihistamine, antipyretic, antitussive, vasodilatory, vitamin. The penetration enhancer is, e.g., a lipophilic solvent, alkyl morpholine, a surfactant, urea.

ADVANTAGE - Any adverse interaction between the enhancer and matrix layer is effectively prevented.

L129 ANSWER 9 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1990-334191 [44] WPIDS
DNN N1990-255469 DNC C1990-145063
TI Trans-dermal delivery device package - includes separate exothermic layer to provide heat to enhance drug absorption through skin.
DC B07 D22 P32
IN ARGAUD, A
PA (ARGA-I) ARGAUD A
CYC 1
PI US 4963360 A 19901016 (199044)*
ADT US 4963360 A US 1988-262879 19881026
PRAI JP 1988-17062U 19880212
IC **A61F002-00**
AB US 4963360 A UPAB: 19930928
An exothermic medical package body comprises: a base sheet; a carrier layer on one side of the base sheet, the carrier layer comprising 4.0-5.0g water, 1-2g gelatin, 2-4g kaolin, 0.1-0.3g antiseptic, 0.2-0.4g AlCl3, 0.1-0.3g propylene glycol, and a medicinal component (I); an exothermic layer, on the opposite surface of the base sheet, which develops heat when brought into contact with air; a separable cover over the carrier layer; an air-permeable film covering the exothermic layer, the film to be brought into contact with human skin to transmit heat from the exothermic layer to the skin; and an air-impermeable packing sheet for sealing and packing the exothermic layer covered by the film. Alternatively, the carrier layer comprises a cloth or fibres impregnated with (I).
USE/ADVANTAGE - Used for transdermal delivery of (I). The heat produced by the exothermic layer improves the absorption of (I) through the skin. The separate layers are more easily formulated, since compatibility problems are avoided.
1/2
FS CPI GMPI
FA AB; GI; DCN
MC CPI: B01-A02; B04-A01; B04-B02B3; B04-C02A1; B04-C03B; B04-C03D; B04-D02; B05-A01B; B05-A03A; B05-C06; B07-D09; B10-A05; B12-M02F; D09-C04B

L129 ANSWER 10 OF 10 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1984-115672 [19] WPIDS
DNN N1984-085515 DNC C1984-048620
TI Hydrogel prodn. by freezing and thawing aq. PVA - giving prod. of increased mechanical strength.
DC A14 A96 B04 B07 C03 D22 P32 P34
IN KINOSHITA, T; NAMBU, M; WATASE, M
PA (NIOC) NIPPON OIL KK
CYC 7
PI EP 107055 A 19840502 (198419)* EN 42p
R: CH DE FR GB LI
JP 59056446 A 19840331 (198419)
US 4808353 A 19890228 (198911)
EP 107055 B 19891206 (198949) EN
R: CH DE FR GB LI
DE 3380922 G 19900111 (199004)
JP 04005457 B 19920131 (199209)
ADT EP 107055 A EP 1983-109491 19830923; JP 59056446 A JP 1982-164870 19820924; US 4808353 A US 1986-816966 19860108; JP 04005457 B JP 1982-164870 19820924
PRAI JP 1982-164870 19820924
REP 5.Jnl.Ref; A3...8520; EP 58497; FR 2107711; JP 56003052; No-SR.Pub; US 3875302; 3.Jnl.Ref
IC A61F001-00; **A61F002-02**; A61K009-70; A61K047-00; A61L015-01; C08J003-02; C08J005-00; C08L029-04; C09K003-00; C09K005-00
AB EP 107055 A UPAB: 19930925
Prodn. comprises (1) freezing an aq. soln.contg. at least 6 wt.% of polyvinyl alcohol (I) (having a deg. of hydrolysis at least 95 mole-% and average polymerisation deg. at least 700) at above -3 deg.C; (2) thawing the frozen mass at up to 55 deg.C; and (3) at least one additional cyclic processing step including the freezing and thawing steps.

The hydrogel has increased mechanical strength compared with prior gels of this type, and the hydrogels are esp. useful in medicinal prepns., as they cause little damage to living tissues. They have high permeability for various substances and improved antithrombotic properties. Vacuum dehydration is not required for prepn. of the hydrogels, and they do not become too soft or have a diminished swelling rate. Chemical treatment and irradiation are not necessary with the hydrogels before they are formed into membranes, artificial organs etc.

0/0

FS CPI GMPI

FA AB

MC CPI: A10-E09B; A12-S; A12-V02; A12-V03; B04-C03B; B11-C04; B12-H02; B12-M03; C04-C03B; C11-C04; C12-H02; C12-M03; D09-C01

ABEQ EP 107055 B UPAB: 19930925

Hydrogel having increased mechanical strength for medical use as an artificial organ or an artificial membrane, said hydrogel being obtainable by a process comprising a freezing step of freezing an aqueous solution containing 6 wt.% or more of a polyvinyl alcohol having a degree of hydrolysis of not less than 95 mol% and an average polymerisation degree of not less than 700 at a temperature of not higher than -3 deg.C to obtain a frozen mass, a thawing step of thawing said frozen mass at a temperature of not higher than 55 deg.C, and at least one additional cyclic processing step including said freezing and thawing steps.

ABEQ US 4808353 A UPAB: 19930925

Prodn. of artificial membranes for surgical use comprises freezing an aq. soln. of PVA (deg. hydrolysis at least 95 mol%; mean deg. of polymerisation not less than 700; at least 6 wt.% polymer content) at temps. not above -3 C; followed by cycle(s) of thawing (at temps. not above 55 C), refreezing and thawing again. Inorganic and/or organic additive(s) which do not hinder gel formation may be present, e.g. heparin.

USE - Prods. are surgical membranes, e.g. diaphragms, pericardia and dura mater, or membranes for the prevention of adhesion between tissues.

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 May 2000 (20000523/PD)
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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2000

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>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

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     (FILE 'WPIDS' ENTERED AT 16:48:23 ON 25 MAY 2000)

     FILE 'USPATFULL' ENTERED AT 16:49:02 ON 25 MAY 2000
L130        9154 S L35
L131        2376 S L130 AND (?IMPLANT? OR IMPLANT?/CT)
L132        6687 S L130 AND (CATTLE OR COW OR CALF OR ANIMAL OR VETERIN? OR SHEE
L133        2120 S L131 AND L132
L134         335 S L65,L68,L73 AND L130
L135         107 S L134 AND L133
L136          44 S L135 AND (CATTLE OR COW OR CALF)/CT,BI
L137          84 S L135 AND (IMMUNIZ? OR IMMUNIS? OR INJECT?)/BI,CT
L138          41 S L137 AND L136
L139           5 S L138 AND (IMPLANT? OR GROWTH HORMON?)/TI

     FILE 'USPATFULL' ENTERED AT 16:53:37 ON 25 MAY 2000

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L139 ANSWER 1 OF 5  USPATFULL
AN      2000:15330  USPATFULL
TI      Polymeric microporous film coated subcutaneous implant
IN      Lee, Jung-Chung, San Jose, CA, United States
        Pushpala, Shamim, Sunnyvale, CA, United States
        Lee, Charles E., Union City, CA, United States
PA      American Home Products Corporation, Madison, NJ, United States (U.S.
        corporation)
PI      US 6022554  20000208
AI      US 1997-990367  19971215 (8)
DT      Utility
EXNAM   Primary Examiner: Page, Thurman K.; Assistant Examiner: Channavajjala,
        Lakshmi
LREP    Darby & Darby
CLMN    Number of Claims: 22
ECL     Exemplary Claim: 21
DRWN    18 Drawing Figure(s); 18 Drawing Page(s)
LN.CNT 1373
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      This invention relates to coating formulations for coating
        sustained-release drug implants. The coating formulations are
        capable of formulations are capable of forming a porous film coat over a
        biologically active agent to provide a release of the active agent at a
        constant rate over a prolonged period of time. The pore forming agent is
        used in the formulation of the invention in the amount effective to
        regulate the release of a biologically active compound at a desired
        rate. Preferably, the effective amount of the pore forming agent
        provides long term delivery of the active agent. The invention also
        provides an improved implant for the sustained administration
        of a biologically active compound suitable for subcutaneous
      implantation. The invention also relates to methods for making
        and using the formulation and the implant of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI      Polymeric microporous film coated subcutaneous implant
AB      This invention relates to coating formulations for coating
        sustained-release drug implants. The coating formulations are
        capable of formulations are capable of forming a porous film coat over a
        biologically active agent to provide a release of the active agent at a
        constant rate over a prolonged period of time. The pore forming agent is
        used in the formulation of the invention in the amount effective to
        regulate the release of a biologically active compound at a desired
        rate. Preferably, the effective amount of the pore forming agent
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provides long term delivery of the active agent. The invention also provides an improved **implant** for the sustained administration of a biologically active compound suitable for subcutaneous **implantation**. The invention also relates to methods for making and using the formulation and the **implant** of the invention.

SUMM This invention relates to a novel coating formulation comprising a pore forming agent for use on sustained-release drug **implants**, an improved **implant** comprising a biologically active agent and a porous coating film capable of releasing the biologically active agent at a constant rate over a prolonged period of time to produce a local or systemic physiological or pharmacological effect, a method for making an **implant** coated with the formulation of the invention and a method for using the coated **implant** to deliver the biologically active agent to a mammal.

SUMM The advantages of employing sustained-release drug **implants** are well known in the art. Many therapeutic agents are rapidly metabolized or cleared from the mammalian body requiring frequent administration of the drug to maintain adequate therapeutic concentration. There is therefore a need for a sustained release **implant** capable of administering an active compound at a relatively constant rate at a level sufficient to maintain an effective concentration.

SUMM A number of sustained-release **implants** are known in the art. Some **implants** are "matrix" type, and comprise an active compound dispersed in a matrix of a carrier material. The carrier material may be either porous or non-porous, solid or semi-solid, and permeable or impermeable to the active compound. Matrix devices may be biodegradable, i.e., they may slowly erode after administration. Alternatively, matrix devices may be nondegradable, and rely on diffusion of the active compound through the walls or pores of the matrix. Matrix devices may be easily prepared, but are not suitable for all compounds. Furthermore, it is difficult to prepare matrix devices that release active compound at a constant rate (i.e., zero order kinetics). Generally, the release rate is typically a function of the active compound's concentration in the matrix.

SUMM U.S. Pat. No. 4,331,651 to Reul discloses a matrix device consisting of a silicone rubber depot for nasal administration to **cattle**. The rubber contains a "release promoting agent" which is liposoluble, scarcely soluble in water, and which may be an alcohol, ester, ether or ketone of 8-60 carbons. The active compound is a steroid, optionally an antibiotic. Preferred steroids are **testosterone** and **trenbolone acetate**, optionally in combination with estrogens such as 17.beta.-**estradiol** and its derivatives.

SUMM Matrix **implants** are also disclosed in P. J. Dziuk, et al., Am. J. Vet. Res. 29, 2413-2417 (1968) "Inhibition and Control of Estrus and Ovulation in Ewes with a Subcutaneous **Implant** of Silicone Rubber Impregnated with a Progestogen"; L. Beck, et al., Drugs, 27, 528-547 (1984) "Controlled-Release Delivery Systems for Hormones"; R. Heitzman, J. **Animal** Sci., 57, 233-238 (1983) "The Absorption, Distribution and Excretion of Anabolic Agents"; J. Wagner, et al., J. **Animal** Sci., 58, 1062-67 (1984) "Effect of Monensin, **Estradiol** Controlled Release **Implants** and Supplement on Performance in Grazing Steers"; N. Scheffrahn, et al., J. **Animal** Sci., 51, 108-109, "Induction of Male Sex Behavior in Ewes Using Silastic **Implants** Containing **Testosterone Propionate**."

SUMM Surface erosion is the major mechanism of delivering the actives to a mammal in a matrix-type **implant**. By applying a layer of water insoluble film around the **implant**, the release rate of the actives could be regulated. Such **implants** are known as "reservoir" type and consist of a central reservoir of active compound

surrounded by a rate controlling membrane. This approach requires an adequate diffusion rate of the actives through the membrane.

SUMM The membrane may be either porous or non-porous, but is not usually biodegradable. It is typically easier to prepare a reservoir **implant** capable of zero order kinetics (independent of active compound concentration), as the release rate often depends only on the surface area of the membrane. However, reservoir devices often suffer from an inadequate rate of delivery given that the membrane surface area required to maintain an effective concentration of active compound is frequently so large that it is impractical to administer the **implant**. Reservoir **implants** are sensitive to rupture and an excessive, possibly lethal, dose of active compound may be released instantaneously.

SUMM UK Patent Application 2,010,676 to Wong, et al. discloses a reservoir **implant** in the form of a flat, heatsealed packet, cylindrical tube or "T" vaginal insert, comprising a rate controlling membrane, specifically ethylene-vinyl acetate copolymer or butylene terephthalate/polytetramethylene ether terephthalate. The active compound is presented in a carrier which is water-imbibing (to maintain, but not increase the size of the **implant**), and viscous to improve drug distribution within the **implant**. These **implants** are useful for administering **progesterone**, **estradiol**, or d-norgestrel.

SUMM Other reservoir **implants** are disclosed in L. Beck, et al., "Controlled-Release Delivery Systems for Hormones" Drugs, 27, 528-547 (1984); W. Greene et al., "Release Rate of **Testosterone** and Estrogens from Polydimethylsiloxane **Implants** for Extended Periods In Vivo Compared with Loss In Vitro" Int. J. Fertil, 23, 128-132 (1978); E. Sommerville, et al., "Plasma **Testosterone** Levels In Adult and Neonatal Female Rats Bearing **Testosterone Propionate**-Filled Silicone Elastomer Capsules for Varying Periods of Time" J. Endocr., 98, 365-371, (1983); U.S. Pat. Nos. 4,210,644; and 4,432,964.

SUMM UK Patent Application 2,154,138A to Roche discloses a hybrid subcutaneous **implant** for **livestock** weight promotion, using silicone rubber with **estradiol** dispersed in the rubber. The **implant** is formed as a substantially hollow cylinder of the silicone rubber, with a core consisting of active ingredients (which may be steroids) dispersed in a biocompatible, biosoluble polymer which dissolves within days of **implantation**. The biocompatible, biosoluble polymer is a mixture of high and low molecular weight polyethylene glycol (PEG). For example, PEG 3,000-10,000 can be used with PEG 200-600. Thus, **estradiol** is released as if from a matrix (the silicone rubber wall), while the second active compound is released from a reservoir.

SUMM U.S. Pat. No. 3,992,518 to Chien discloses another hybrid **implant** comprising a membrane-wrapped silicone rubber matrix. The rubber matrix is prepared by forming an emulsion of rubber monomer and active compound in aqueous solution with a hydrophilic co-solvent, then crosslinking the monomer to form "microsealed compartments" containing the active compound in solution. The resulting matrix is then coated with a rate-controlling membrane. The rate-controlling membrane may be silicone rubber, ethylene/vinyl acetate, polyethylene terephthalate, butyl rubber, etc. The active compound is in a solution of water and a hydrophilic cosolvent not soluble in the rubber matrix. The hydrophilic cosolvent may be polyethylene glycol, propylene glycol, butylene glycol, etc., with PEG 400 preferred at a concentration of 20-70%. Active compounds disclosed include ethynodiol diacetate, ethylnyl **estradiol**, estrone, **estradiol**, other estrogens, **progesterone**, and **testosterone**.

SUMM U.S. Pat. No. 5,342,622 to Williams et al. discloses a pharmaceutical or **veterinary implant** comprising a peptide or protein and an excipient encased within a polymeric coating which is permeable and swellable. The coat forms a release rate limiting barrier and is preferably a neutral copolymer based on poly(meth) acrylic acid esters. One such suitable coating is "Eudragit E30D" (available from Rohm Pharma, GmbH).

SUMM U.S. Pat. No. 5,091,185 to Castillo et al. discloses a coated **veterinary implant** comprising a solid core of a growth hormone and a coating of polyvinylalcohol continuously enveloping the core.

SUMM U.S. Pat. No. 4,666,704 to Shalati et al. teaches an **implant** composition comprising (i) a core of a macromolecular drug and a water insoluble polymer and (ii) a pore-forming membrane with uniformly distributed pore-forming agent such as dimethyl and diethyl tartrate and lower partial esters of citric acid.

SUMM The mode of administration is usually critical to the design of a sustained release **implant**. The **implant** must be adapted to the appropriate biological environment in which it is used. For example, a device for subcutaneous **implantation** must be non-irritating, mechanically strong to withstand flexion or impact, and should provide long term delivery of the drug. In contrast, a device for oral administration must be designed for resistance to gastric acidity and sensitivity to pH change and short term delivery of drugs. Coatings suitable for gastric environments of acid pH that provide short term delivery of drugs, are known in the art. For example, Munday and Fassihi, Int. J. Pharm, 52: 109-114 (1989) disclose an oral control delivery tablet coated with insoluble polymers such as Eudragit RS and RL and a pore forming agent PEG 1540. This coating allows for 100% drug release within 10 hours after administration. Similarly, Marini et al., Drug Dev. Ind. Pharm, 17:865-877 (1991) and Muhamed et al., Drug Dev. Ind. Pharm, 17:2497-2509 (1991) disclose oral dosage forms comprising a coating with PEG. Both references show that such coating allows drug delivery within hours after administration.

SUMM It has now been surprisingly discovered that coatings containing PEG can be successfully used to make long term sustained release drug **implants**. Such PEG coatings unexpectedly increase the life of **implants**. For example, most **cattle implants** on the market have the release duration between 60-90 days. In order to continue promoting the growth of an **animal**, **reimplantation** of another dose is essential. R. L. Preston and J. R. Rains, FEEDSTUFFS, January 1993, pp. 18-20. Using **implants** prepared according to the present invention, the life of **implants** can be extended to over 150 days thus eliminating the need for repeated **implantation**. Another advantage of the coating technology of the present invention is that it offers a simple way of extending the duration of an **implant** without dramatic re-formulation of existing products and excessive costs. A third advantage to the present invention is that by varying amount of pore forming agent, the duration of the **implant** may be tailored to the desired target.

DRWD FIG. 1 is a graph showing in vitro diffusion of **trenbolone acetate** (TBA) and **estradiol benzoate** (EB) through various polymers.

DRWD FIG. 7a is a graph showing TBA depletion (represented by percent TBA remaining in the **implant**) depending on varying concentrations of PEG 8000.

DRWD FIG. 7c is a graph showing EB depletion (represented by percent EB remaining in the **implant**) depending on varying PEG 8000 concentrations.

DRWD FIG. 8a is a graph showing depletion of actives (represented by percent

active remaining in the **implant**) depending on the coating thickness.

DRWD FIG. 10 is a graph showing a comparison of the release rates (represented by the average release rate mg/day) of TBA/EB **implants** currently available on the market and TBA/EB **implants** prepared according to the present invention.

DRWD FIG. 12 is a graph showing correlation between the concentration of PEG 8000 in the coating and the lifetime of the **implant**.

DRWD FIG. 13 is a graph showing correlation between the lifetime duration of an **implant** and the percent of TBA dissolved in vitro after 120 hours.

DETD This invention encompasses novel coating formulations for coating sustained-release drug **implants**. The coating formulations are capable of forming a porous film over a biologically active agent to provide a release of the active agent at a constant rate over a prolonged period of time. The formulation of the invention comprises a water soluble pore forming agent, such as polyethylene glycol, mixed with a water insoluble polymer. The pore forming agent is used in the formulation of the invention in the amount effective to regulate the release of a biologically active compound at a desired rate. The pore forming agent leaches out through the film in situ, and thus creates a perforated film around the **implants** which regulates the release rate of actives through micro-channels. Preferably, the effective amount of the pore forming agent provides long term delivery of the active agent.

DETD In another aspect, the invention provides an improved **implant** for the sustained administration of a biologically active compound, suitable for subcutaneous **implantation**, which comprises an effective amount of a biologically active agent and a sufficient amount of the porous film coating. The porous film coating comprises a water soluble pore forming agent, such as polyethylene glycol, and water insoluble polymers and is prepared by coating the biologically active compound with the formulation of the invention. The porous film comprises the pore forming agent in the amount effective to increase the useful life of the **implant**.

DETD In a further aspect, the invention provides for a method for making the formulation and the **implant** of the invention.

DETD In yet another aspect, the invention provides for a method of treating a mammal by **implanting** the improved **implant** of the invention.

DETD The term "biologically active compound" as used herein refers to a compound useful for effecting some beneficial change in the subject to which it is administered. For example, "biologically active compounds" within the scope of this definition include steroid hormones, prostaglandins, vitamins, antibiotics, antiinflammatory agents, chemotherapeutic agents, cardiovascular and antihypertensive agents. Preferred biologically active compounds within the invention are steroid hormones useful for promoting weight gain in **livestock**, especially **estradiol benzoate**, **trenbolone acetate**, **progesterone**, and **testosterone propionate**.

DETD The term "pharmaceutically acceptable steroid" refers to a steroid hormone suitable for parenteral administration to a mammal, particularly a human. Suitable steroids include levonorgestrel, **estradiol** 17.beta.-, **testosterone**, **testosterone propionate**, and ethinyl **estradiol**.

DETD The term "effective amount" as applied to the biologically active compound refers to that amount which is sufficient to effect the desired change in the subject. For example, where the desired effect is an increase in weight gain of **livestock**, the "effective amount" is a "**livestock** weight gain-promoting" amount, and will vary depending on the **animal** species. If the desired effect is human contraception, an effective amount is that amount sufficient to result in contraception, which can be easily determined by one of ordinary skill in the art.

DETD The term "effective amount" as applied to the pore forming agent refers

to that amount which is sufficient to regulate the release of a biologically active agent at a desired rate for a desired period of time. For example, where the desired effect is an increase in weight gain of **livestock** by using a single **implant** during the productive cycle, the "effective amount" is the amount that will extend the release over a period of more than 150 days. This "effective amount" can be determined based on the teaching in this specification and the general knowledge in the art.

DETD The term "sufficient amount" as applied to the coating film formulation refers to the amount of surface area of membrane required to effect a flux of biologically active compound sufficient to achieve the desired purpose. The area necessary may be determined and adjusted directly by measuring the release obtained for the particular active compound. The surface area of the coating is that amount of membrane necessary to completely encapsulate the biologically active compound. The surface area depends on the geometry of the **implant**. Preferably, the surface area is minimized where possible, to reduce the size of the **implant**. In one preferred embodiment of the invention, suitable for **implantation** in **cattle**, the **implant** device is a cylinder measuring approximately 3.2 mm by 30.5 mm and having a surface area of 3.227 cm.sup.2.

DETD The term "treatment" as used herein covers any treatment of a disease in an **animal** (including a human), and includes: (i) preventing the disease from occurring; (ii) inhibiting the disease, i.e., arresting its development; (iii) relieving the disease, i.e., causing regression of the disease; or (iv) modifying normal biological activity such as in the case of promotion of weight gain or contraception.

DETD The present invention provides novel coating formulations for coating sustained-release drug **implants**. The coating formulations are capable of forming a porous film over a biologically active agent to provide release of the active agent at a constant rate over a prolonged period of time. The formulation of the invention comprises a water soluble pore forming agent, such as polyethylene glycol, mixed with water insoluble polymers.

DETD The pore forming agent is used in the formulation of the invention in the amount effective to regulate the release of a biologically active compound at a desired rate. Preferably, the effective amount of the pore forming agent provides long term delivery of the active agent thus increasing the useful life of a sustained-release drug **implant** . The effective amount of the pore forming agent will depend on the desired rate and duration of the release and the ability to form a continuous microporous film during the coating process.

DETD There is a good correlation between the dissolution rate of active agents and the amount of pore forming agent incorporated in the coating film based on in vitro and in vivo studies shown in the Examples. Depending on the desired length of release, the PEG concentration ranges can be adjusted using correlation coefficients provided in the Examples. For example, in vivo duration of a coated **implant** may be predicted simply from the in vitro dissolution rate of the active agent at the 120-hour time point. Using the coating formulation of this invention, it is possible to prolong the 100-day duration of **implants** currently available on the market to a desired, longer duration of 150, 180 or 200 days.

DETD A polymer suitable for use in this invention is a polymer which is capable of forming a continuous coating film during the process of spraying and drying with a pore forming agent. The rate controlling film prepared with such a polymer is very stable during **implantation** . The film should have enough strength to withstand tear and inner osmotic pressure, and have the stability not to swell or hydrate during the **implantation** life.

DETD Another aspect of the invention is an improved **implant** for sustained administration of a biologically active compound, suitable for subcutaneous **implantation** which comprises an effective amount of a biologically active compound and a sufficient amount of a porous coating film which completely encapsulates said biologically active compound. In a preferred embodiment, the **implant** of the

invention comprises the biologically active compound in the form of a pellet or a plurality of pellets, for example three to fifteen pellets. An **implant** in which said biologically active agent comprises an estrogen derivative in combination with a progestogen or an androgenic agent is also preferred. More preferably, said estrogen derivative is **estradiol benzoate**, particularly where the **estradiol benzoate** is in combination with **progesterone**, **testosterone propionate**, or **trenbolone acetate**. One of the preferred embodiments is an improved **implant** comprising **estradiol benzoate** and **trenbolone acetate** for long term delivery having a lifetime duration over 100 days and preferably over 180+ days.

DETD The manufacture of an **implant** of the invention may be accomplished through a variety of methods known in the art, for example those disclosed in the U.S. Pat. No. 5,035,891.

DETD This invention also provides for an improved **implant** further comprising an amount of an antibiotic present within the solid formulation or on the outer surface of the porous coating film in an amount sufficient to prevent infection associated with **implantation** of said **implant**. Such antibiotic may be applied to the **implant** by methods known in the art, and for example as disclosed in U.K. Application No: 2,136,688A to Ferguson.

DETD The amount of a biologically active compound in the improved **implant** of the invention may be as is commonly known and used in the art. For example, steroid containing pellets can contain the amount disclosed in the U.S. Pat. No. 5,035,891 to Runkel et al. According to one of the embodiments of the invention, an **implant** may comprise eight pellets comprising a total of 28 mg **estradiol benzoate** and 200 mg **trenbolone acetate**. According to another embodiment, an **implant** containing a porous coating film of the invention may comprise six pellets and a total of 24 mg **estradiol** and 120 mg **trenbolone acetate**.

DETD It is within the knowledge and skill of those skilled in the art to determine the amount of an active agent used in the **implant**. Generally, the amount of a biologically active compound administered via the **implant** of the invention will vary depending on the identity of the compound; the size, age, weight, and species of the subject to be treated; the severity of the condition or the magnitude of the effect desired, and so forth. These parameters are easily determined and factored by one of ordinary skill in the art. For example, a representative **implant** of the invention suitable for promoting growth in steers contains a combination of about 200 mg of **progesterone** and about 20 mg of **estradiol benzoate** as the biologically active compound. A representative **implant** suitable for promoting growth in heifers contains a combination of about 200 mg of **testosterone propionate** and about 20 mg **estradiol benzoate** as the biologically active compound.

DETD Another aspect of the invention is a method for administering a biologically active compound to a subject in need thereof over an extended time period which comprises **implanting** subcutaneously the **implant** of the invention. One of preferred embodiments of the invention is the method that comprises subcutaneously administering an **implant** comprising an effective amount of a weight gain promoting steroid, and a sufficient amount of a porous coating film of the invention. In another preferred method, an **implant** comprising a pellet or plurality of pellets comprising 20-1,000 mg of progesteronne, **testosterone propionate**, or **trenbolone acetate**, 2-100 mg of **estradiol benzoate**, 3.23 cm.sup.2 of a porous film comprising PEG 8000 as a pore forming agent.

DETD An improved **implant** of the invention which is administered to promote growth in **cattle** may be **implanted** subcutaneously using a hollow needle **implanting** gun, for

example the type disclosed in U.S. Pat. No. 4,474,572, incorporated herein by reference. The diameter of the needle may be adjusted to correspond to the size of the **implant** used. For administration to **cattle**, the **implant** is placed subcutaneously in the middle third of the subject's ear. Alternative sites of subcutaneous administration include the nape of the subject's neck and the axillary region. Other devices of the invention, when scaled to a suitable size, are suitable for similar **implantation** in **sheep**, **swine** or **horses**.

DETD Another aspect of the invention is a method for administering a pharmaceutically acceptable steroid to a mammal to effect contraception, estrogen replacement therapy, or breast cancer treatment, which method comprises subcutaneously **implanting** a reservoir **implant** comprising an effective amount of a pharmaceutically acceptable steroid. Another embodiment of the invention comprises a contraceptive or chemotherapeutic **implant** for humans. The microporous film suitable for use in humans comprise bio-erodible polymers such as high molecular weight PLGA or orthoesters.

DETD The sustained-release **implants** of the invention are designed for subcutaneous **implantation**, but may alternatively be administered to other body cavities, for example, vaginally, nasally and sublingually.

DETD Pharmaceutical excipient can also be used in the **implants** of the invention. Suitable excipient are well known in the art and include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride and dried skim milk.

DETD Various subcutaneous **implants** containing **trenbolone acetate** (TBA) and **estradiol benzoate** (EB) as biologically active agents coated with a polymeric microporous film of the invention were prepared and tested in vitro and in vivo to determine the duration and rate of release of active agents. A good correlation between the release rate of actives, i.e., TBA and EB, duration of the **implant** and amount of PEG 8000 incorporated in the film coating was observed.

DETD All **implants** used in the experiment consisted of 8 pellets, each comprising 25 mg TBA and 3.5 mg EB. Each **implant** was coated with a layer of a polymeric film. Two sets of film formulations (designated F1-F10 and A-F) were prepared from Aquacoat.RTM. and Eudragit.RTM. aqueous dispersions with Polyethylene Glycol (PEG) 8000 as a pore forming agent. The percentage of ingredients in each film formulation were as outlined in the following Table A.

DETD The TBA and EB long term release rates from **implants** coated with test film formulations were determined in vitro. Ten film coating formulations designated F1 to F10 in the above table were used for this study. As indicated, the coating formulations consisted of aqueous polymer dispersions (such as Aquacoat ECD 30, Eudragit NE 30D or Eudragit RS 30D) mixed with PEG 8000, a pore forming agent. The concentration of PEG 8000 was in the range from 0-40%. A thin coat comprising 5% and a medium thick coat comprising 10% by weight of an **implant** were also tested to evaluate the integrity of the coating film during the period of the TBA and EB release.

DETD TABLE 1

AVERAGE IN VITRO CUMULATIVE RELEASE (%) AND RELEASE RATE (MG/DAY) OF **TRENBOLONE ACETATE** FROM VARIOUS LONG ACTING TBA/EB PREPARATIONS

F#	COATING POLYMER	% PEG	% COAT	RELEASE TIME (DAYS) 1	2	4	6	7	9	14	18	21	25	29
AVERAGE CUMULATIVE RELEASE (%) OF TBA														
F1	AQUACOAT .RTM. ECD 30	0.0	5.0	1.01										

1.15
1.38
1.38
1.72
1.92
2.44
2.90
3.23
3.64
4.21

F2 AQUACOAT .RTM. ECD 30
10.0
5.0 1.12
1.35
1.74
1.74
2.23
2.57
3.51
4.14
5.26
6.72
7.89

F3 AQUACOAT .RTM. ECD 30
30.0
5.0 3.15
5.47
9.87
15.34
17.52
22.38
36.22
46.36
54.12
62.07
69.14

F4 AQUACOAT .RTM. ECD 30
40.0
5.0 7.37
14.70
27.86
40.47
45.12
54.42
72.57
83.20
89.38
94.40
96.43

F5 AQUACOAT .RTM. ECD 30
30.0
10.0 3.12
4.95
8.65
12.49
14.13
17.70
27.33
35.07
40.71
47.31
53.81

F6 EUDRAGIT .RTM. NE 30D
0.0 5.0 0.71
1.41
3.11

3.11
5.92
8.04
14.02
19.27
23.03
27.59
32.06

F7 EUDRAGIT .RTM. NE 30D
30.0
5.0 5.17
9.84
25.61
35.51
38.39
44.48
58.92
69.40
76.59
84.72
91.70

F8 EUDRAGIT .RTM. NE 30D
30.0
10.0 2.85
5.45
10.34
15.14
17.22
21.35
32.42
40.75
46.38
53.05
59.16

F9 EUDRAGIT .RTM. RS 30D
0.0 5.0 0.05
0.11
0.21
0.21
0.44
0.64
1.32
2.05
2.65
3.56
4.48

F10
EUDRAGIT .RTM. RS 30D
30.0
5.0 2.78
5.51
10.51
15.37
17.24
21.41
32.59
41.07
46.93
54.42
61.01

AVERAGE RELEASE RATE (MG/DAY) OF TBA
F1 AQUACOAT .RTM. ECD 30
0.0 5.0 1.01
0.16
0.11
0.00

0.11
0.10
0.11
0.12
0.11
0.10
0.14

F2 AQUACOAT .RTM. ECD 30
10.0
5.0 1.13
0.23
0.20
0.00
0.17
0.17
0.19
0.16
0.38
0.37
0.30

F3 AQUACOAT .RTM. ECD 30
30.0
5.0 3.19
2.35
2.23
2.77
2.21
2.46
2.81
2.57
2.62
2.02
1.79

F4 AQUACOAT .RTM. ECD 30
40.0
5.0 7.46
7.43
6.66
6.38
4.71
4.71
3.68
2.69
2.08
1.27
0.52

F5 AQUACOAT .RTM. ECD 30
30.0
10.0 3.12
1.84
1.85
1.92
1.64
1.79
1.93
1.94
1.89
1.66
1.63

F6 EUDRAGIT .RTM. NE 30D
0.0 5.0 0.72
0.70
0.86
0.00
0.95
1.08

1.21
1.33
1.27
1.16
1.14

F7 EUDRAGIT .RTM. NE 30D
30.0
5.0 5.21
4.71
7.96
4.99
2.91
3.28
2.83
2.64
2.42
2.05
1.76

F8 EUDRAGIT .RTM. NE 30D
30.0
10.0 2.85
2.60
2.44
2.40
2.08
2.07
2.21
2.08
1.88
1.67
1.53

F9 EUDRAGIT .RTM. RS 30D
0.0 5.0 0.05
0.05
0.06
0.00
0.07
0.10
0.14
0.18
0.20
0.23
0.23

F10
EUDRAGIT .RTM. RS 30D
30.0
5.0 2.80
2.76
2.52
2.46
1.89
2.10
2.25
2.14
1.97
1.89
1.66

DETD TABLE 2

AVERAGE IN VITRO CUMULATIVE RELEASE (%) AND RELEASE RATE (MG/DAY)
OF **ESTRADIOL BENZOATE** FROM VARIOUS LONG ACTING TBA/EB
PREPARATIONS

RELEASE TIME (DAYS)

F# COATING POLYMER
% PEG

% COAT
1 2 4 6 7 9 14 18 21 25 29

AVERAGE CUMULATIVE RELEASE (%) OF EB

F1 AQUACOAT .RTM. ECD 30

0.0 5.0 0.67
0.67
0.67
0.67
0.67
0.67
0.81
0.94
1.06
1.30

F2 AQUACOAT .RTM. ECD 30

10.0
5.0 0.89
0.89
0.89
0.89
1.01
10.01
1.34
1.48
2.03
2.77
3.35

F3 AQUACOAT .RTM. ECD 30

30.0
5.0 2.34
3.89
6.98
10.76
12.29
15.69
24.87
30.69
35.61
40.16
45.01

F4 AQUACOAT .RTM. ECD 30

40.0
5.0 5.18
10.61
20.86
30.56
31.21
41.69
54.91
62.22
68.04
72.77
76.60

F5 AQUACOAT .RTM. ECD 30

30.0
10.0 2.32
3.47
5.98
8.54
9.72
12.14
17.58
21.64
25.25

28.73
32.44

F6 EUDRAGIT .RTM. NE 30D
0.0 5.0 0.04
0.09
0.57
0.57
1.67
2.56
5.11
6.92
8.49
10.11
12.01

F7 EUDRAGIT .RTM. NE 30D
30.0
5.0 3.02
5.93
11.77
16.82
18.68
22.97
30.51
36.01
40.61
45.13
49.71

F8 EUDRAGIT .RTM. NE 30D
30.0
10.0 0.61
1.19
2.31
3.37
3.83
4.76
6.97
8.42
9.63
10.83
12.23

F9 EUDRAGIT .RTM. RS 30D
0.0 5.0 0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.00

F10
EUDRAGIT .RTM. RS 30D
30.0
5.0 0.61
1.19
2.31
3.34
3.74
4.71
6.63
8.06
9.34
10.69
12.06

AVERAGE RELEASE RATE (MG/DAY) OF EB
F1 AQUACOAT .RTM. ECD 30
0.0 5.0 0.09
0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.01
0.00
0.01
F2 AQUACOAT .RTM. ECD 30
10.0
5.0 0.13
0.00
0.00
0.00
0.01
0.00
0.01
0.00
0.03
0.03
0.02
F3 AQUACOAT .RTM. ECD 30
30.0
5.0 0.33
0.22
0.22
0.27
0.22
0.24
0.26
0.21
0.23
0.16
0.17
F4 AQUACOAT .RTM. ECD 30
40.0
5.0 0.74
0.77
0.73
0.89
0.52
0.53
0.37
0.28
0.28
0.17
0.14
F5 AQUACOAT .RTM. ECD 30
30.0
10.0 0.33
0.16
0.18
0.18
0.16
0.17
0.15
0.14
0.17
0.12
0.13
F6 EUDRAGIT .RTM. NE 30D

0.0 5.0 0.0t
0.01
0.03
0.00
0.05
0.06
0.07
0.06
0.07
0.06
0.07

F7 EUDRAGIT .RTM. NE 30D
30.0
5.0 0.43
0.41
0.41
0.36
0.26
0.30
0.21
0.19
0.22
0.16
0.16

F8 EUDRAGIT .RTM. NE 30D
30.0
10.0 0;08
0.08
0.08
0.07
0.06
0.07
0.06
0.05
0.06
0.04
0.05

F9 EUDRAGIT .RTM. RS 30D
0.0 5.0 0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.00

F10
EUDRAGIT .RTM. RS 30D
30.0
5.0 0.08
0.08
0.08
0.07
0.06
0.07
0.05
0.05
0.06
0.05
0.05

DETD The TBA and EB dissolution rates for **implants** coated with test film formulations were determined in vitro. Six coating formulations

(formulations A to F in Table A) were used for this study. As indicated in Table A, the coating formulations consisted of aqueous polymer dispersions (such as Aquacoat ECD 30 or Eudragit RS 30D) mixed with PEG 8000 as a pore forming agent. The concentration of PEG 8000 was in the range from 25-30%. A thin coat comprising 5% and a medium thick coat comprising 10% by weight of an **implant** were also tested to evaluate the integrity of the coating film during the period of TBA and EB dissolution.

DETD The 10% and 15% coatings with 30% PEG 8000 had very similar dissolution profiles for both TBA and EB throughout the 5-day testing. The dissolution rate was slower for Eudragit RS 30D-coated **implants** than for Aquacoat ECD 30-coated **implants** at the same amount of PEG 8000 (30%). This difference can be attributed to the elasticity of the acrylic/methacrylic copolymer.

DETD In vivo **Animal** Study

DETD The TBA and EB release in vivo was determined using 24 steers. Pellets containing TBA and EB were coated with six film formulations designated as formulations A to F in Table A and **injected** subcutaneously in the ears of test steers. Each **animal** received 6 **implants** (three in each ear), one of each formulation A to F. The total duration of the study was 180 days and **implants** were excised and removed at four time points, at day 45, 90, 135 and 180. Six **implants** per each formulation (from six **animals**) were removed at each time interval.

DETD Thickness (10 and 15% coating) did not affect the release of the actives but did add consistency to the release rates for the entire **implantation** period. FIGS. 8a and 8b show release profiles for **implants** with different levels of coating.

DETD Eudragit RS 30D formulation showed a slower release rate for both actives in comparison to Aquacoat formulations containing the same amount of PEG 8000. This is illustrated in FIG. 9a. It is noted that, the Aquacoat coated pellets with 25% PEG had a much higher depletion rate at day 90 than expected. However, this may be due to a burst in the film caused by the high osmotic pressure generated inside the capsule during the earlier **implantation** stage.

DETD At day 180, about 5-20% of TBA and 10-30% of EB were recovered from test **implants**. Aquacoat coated **implants** with 30% or 35% PEG showed the most desired release pattern, i.e., the longest duration of release.

DETD FIG. 10 shows the comparison of the release rates from the current TBA/EB **implant** and the coated **implants** with Aquacoat ECD 30, 30% PEG and 15% overall coating. These results establish that the duration of the current TBA/EB **implants** can be prolonged beyond 180 days by using the coating formulation of the present invention.

DETD The effect of the PEG 8000 concentration in the coating formulation on the in vitro dissolution rates of TBA (%) is shown in FIG. 11. Also, a correlation between the extrapolated in vivo duration of the **implants** and the concentration (%) of PEG 8000 in the coating film is shown in FIG. 12. From the correlation, the most desirable coating formulation to obtain a 200-day **implant** duration comprises Aquacoat ECD 30, approximately 32% PEG and at least 15% overall coating by weight.

DETD Finally, the possibility of using in vitro dissolution rates of coated **implants** obtained at the 120-hour time point to predict in vivo duration of the coated **implants** was investigated. A good correlation was observed as shown in FIG. 13.

DETD TABLE 4

IN VIVO DEPLETION OF VARIOUS TBA/EB LONG ACTING PREPARATIONS IN STEERS

F#	COATING POLYMER	% PEG	% COAT	**IMPLANTATION** PERIOD (DAYS) 45 (S.D.)

90 (S.D.)
135
(S.D.)
180
(S.D.)

PERCENT TBA REMAINING
A AQUACOAT .RTM. ECD 30
25.0
10.0 91.68
4.57
44.48
24.39
24.78
14.40
18.37
13.43
B AQUACOAT .RTM. ECD 30
30.0
10.0 80.83
8.96
49.61
20.62
25.24
23.24
7.67
6.48
C AQUACOAT .RTM. ECD 30
35.0
10.0 58.68
8.91
40.00
7.12
18.76
17.06
5.65
3.55
D AQUACOAT .RTM. ECD 30
40.0
10.0 56.44
6.05
21.79
12.57
5.31
6.61
2.60
4.76
E EUDRAGIT .RTM. RS 30D
30.0
10.0 94.21
4.49
64.18
16.84
31.46
17.79
11.01
7.84
F AQUACOAT .RTM. ECD 30
35.0
15.0 80.52
3.97
51.99
9.21
28.97
20.28
12.85

12.76

PERCENT EB REMAINING
A AQUACOAT .RTM. ECD 30
25.0
10.0 96.82
5.51
54.05
26.57
34.69
16.29
29.73
17.33
B AQUACOAT .RTM. ECD 30
30.0
10.0 89.84
8.37
69.24
22.50
33.61
29.50
25.92
15.56
C AQUACOAT .RTM. ECD 30
35.0
10.0 73.78
9.58
60.52
8.24
26.33
16.40
20.96
5.63
D AQUACOAT .RTM. ECD 30
40.0
10.0 67.19
11.04
30.41
14.91
19.59
25.85
7.67
9.45
E EUDRAGIT .RTM. RS 30D
30.0
10.0 94.90
4.97
74.96
20.13
41.82
17.89
26.87
13.77
F AQUACOAT .RTM. ECD 30
35.0
15.0 87.68
4.91
61.44
11.45
40.29
21.93
25.49
25.49

DETD TABLE 5

IN VIVO DEPLETION OF VARIOUS TBA/EB LONG ACTING PREPARATIONS

IN STEERS

IMPLANTATION PERIOD
(DAYS)

F# COATING POLYMER
% PEG
% COAT
. 45 90 135
180

TBA DEPLETION RATE (MG/DAY)
A AQUACOAT .RTM. ECD 30
25.0
10.0 0.345
1.945
0.835
0.266
B AQUACOAT .RTM. ECD 30
30.0
10.0 0.854
1.287
0.938
0.724
C AQUACOAT .RTM. ECD 30
35.0
10.0 1.808
0.701
0.887
0.547
D AQUACOAT .RTM. ECD 30
40.0
10.0 1.836
1.432
0.681
0.112
E EUDRAGIT .RTM. RS 30D
30.0
10.0 0.384
1.113
1.393
0.828
F AQUACOAT .RTM. ECD 30
35.0
15.0 0.871
1.165
0.921
0.673

EB DEPLETION RATE (MG/DAY)
A AQUACOAT .RTM. ECD 30
25.0
10.0 0.015
0.261
0.117
0.029
B AQUACOAT .RTM. ECD 30
30.0
10.0 0.071
0.126
0.202
0.046
C AQUACOAT .RTM. ECD 30
35.0
10.0 0.175
0.066
0.209
0.033
D AQUACOAT .RTM. ECD 30

40.0
10.0 0.196
0.220
0.065
0.072

E EUDRAGIT .RTM. RS 30D
30.0
10.0 0.058
0.094
0.208
0.086

F AQUACOAT .RTM. ECD 30
35.0
15.0 0.084
0.156
0.122
0.090

CLM What is claimed is:

1. A long term sustained-release **implant** comprising: (i) an effective amount of a biologically active agent; and (ii) a film coat comprising a mixture of a water insoluble polymer and a polyethylene glycol as a water soluble pore forming agent, said polyethylene glycol being in an amount effective to regulate the release of said biologically active compound, wherein the duration of sustained release of the **implant** in a mammal is greater than 100 days.

2. The **implant** of claim 1 wherein the molecular weight of said polyethylene glycol is from about 200 to about 20,000.

3. The **implant** of claim 1 wherein the molecular weight of said polyethylene glycol is about 8,000.

4. The **implant** of claim 1 wherein said effective amount of said polyethylene glycol is from about 10% to about 50% per dry weight of said film coat.

5. The **implant** of claim 1 wherein said water insoluble polymer is cellulose ethyl ether, or poly(ethylacrylate, methylmethacrylate, trimethylammonioethyl-methacrylate).

6. The **implant** of claim 1 wherein said biologically active compound is a steroid hormone.

7. The **implant** of claim 6 wherein said steroid hormone comprises an estrogen derivative in combination with a progestogen, and androgen or a combination thereof.

8. The **implant** of claim 1 wherein said biologically active compound is a steroid hormone in an amount effective to promote **livestock** weight gain and said polyethylene glycol has the molecular weight of about 8,000 and is present in the amount of between 10% to 50% per dry weight of the coating film.

9. The **implant** of claim 8 wherein the thickness of said film coat is between 5 to 50 .mu.m.

10. The **implant** of claim 8 wherein said steroid hormone is **estradiol benzoate** and **trenbolone acetate**.

11. A method for treating a mammal comprising **implanting** into the body of said mammal a long term sustained-release **implant** comprising: (i) an effective amount of a biologically active agent; and (i) a film coat comprising a mixture of a water insoluble polymer and a polyethylene glycol as a water soluble pore forming agent, said

polyethylene glycol being in an amount effective to regulate the release of said biologically active compound, wherein duration of sustained release of the **implant** in the mammal is greater than 100 days.

18. The method of claim 11 wherein said biologically active compound is a steroid hormone in an amount effective to promote **livestock** weight gain and said polyethylene glycol has the molecular weight of about 8,000 and is present in the amount of between 10% to 50% per dry weight of the film coat.

20. The method of claim 18 wherein said steroid hormone is **estradiol benzoate** and **trenbolone acetate**.

21. A long term sustained-release **implant** comprising: (i) an effective amount of a biologically active agent; and (ii) a film coat comprising a mixture of a water insoluble polymer and a water soluble pore forming agent, said pore forming agent being in an amount effective to regulate the release of said biologically active compound, wherein the duration of sustained release of the **implant** in a mammal is greater than 150 days.

22. The **implant** of claim 21 wherein said water soluble pore forming agent is polyethylene glycol, polypropylene glycol, sugar, salt, poloxamers, or polyvinyl alcohol.

IT **50-50-0**, Estradiol benzoate **9004-57-3**, Cellulose ethyl ether 9010-88-2, Eudragit NE30D **10161-34-9**, Trenbolone acetate 33434-24-1, Eudragit RS30D
(polymeric microporous film coated s.c. implants)

L139 ANSWER 2 OF 5 USPATFULL
AN 1998:44907 USPATFULL
TI Sustained release formulation of **animal growth hormone** and process for preparation thereof
IN Kim, Ae-Ri, Daejeon, Korea, Republic of
Kim, Nam-Joong, Daejeon, Korea, Republic of
Jung, Min-Hee, Daejeon, Korea, Republic of
PA LG Chemical Ltd., Seoul, Korea, Republic of (non-U.S. corporation)
PI US 5744163 19980428
AI US 1996-749912 19961113 (8)
PRAI KR 1996-341 19960110
DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Benston, Jr., William E.
LREP Anderson, Kill & Olick, P.C.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 405
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a sustained-release formulation of an **animal** growth hormone and a process for preparation thereof, comprising a step to produce solid pellets by mixing an **animal** growth hormone and an excipient in accordance with a direct tabletting method and a step to coat the pellets with a film comprising a biodegradable polymer and a poloxamer. The thus obtained formulation has small initial drug release, and shows a continuous and uniform effect when administered. Further, the formulation of the present invention may be produced economically in a large scale.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Sustained release formulation of **animal growth hormone** and process for preparation thereof
AB The present invention relates to a sustained-release formulation of an **animal** growth hormone and a process for preparation thereof,

comprising a step to produce solid pellets by mixing an **animal** growth hormone and an excipient in accordance with a direct tabletting method and a step to coat the pellets with a film comprising a biodegradable polymer and a poloxamer. The thus obtained formulation has small initial drug release, and shows a continuous and uniform effect when administered. Further, the formulation of the present invention may be produced economically in a large scale.

SUMM The present invention relates to an **animal** growth hormone formulation which continuously releases an effective and steady amount of the hormone over a period of more than 1 week when **implanted** in an **animal** body.

SUMM An **animal** growth hormone is a protein, and it is therefore decomposed and absorbed by digestive enzymes when orally administered by mixing with feed. In order to maintain an effective concentration of the hormone in blood, it must thus be administered by a non-oral method, e.g., intramuscular or subcutaneous **injection**.

SUMM **Animal** growth hormones can now be produced in a large scale by the DNA recombination techniques, and it has been demonstrated that porcine **somatotropin** produced by such techniques improves the feed efficiency and reduces the fat thickness of **pig**'s back. However, the currently available daily **injection** formulation may not be suitable for treating a large number of **pigs** in a big farm. Accordingly, a sustained-release formulation, which does not require daily administration and does not release an excessive amount of the drug at the initial stage, may be most preferable for practical application.

SUMM U.S. patent application Ser. No. 4,863,736 discloses a formulation produced by coating all but one side of a solid pellet of porcine **somatotropin** prepared without the use of a binding agent. However, this formulation containing no binding agent has the problem of swelling caused by osmotic pressure when it contacts with water.

SUMM European Patent No. 0 462 959 discloses a method for making solid pellets from porcine **somatotropin** and a copper complex, and then, coating them with an aqueous solution of polyvinyl alcohol. Because an **animal** growth hormone is a protein, a method for preparing a composition thereof must not involve conditions which may cause denaturation of the protein. Proteins are known to be unstable in aqueous solutions and may lose activity when they contact with water at a high temperature, but they are quite stable in anhydrous organic solvent [D. B. Volkin and C. R. Middaugh, The effect of temperature on protein structure in Pharmaceutical Biotechnology, Vol. 2; Stability of Protein Pharmaceuticals, Part A, p215-247].

SUMM Buonomo et al. and Klindt et al. have reported a miniosmotic pump containing a porcine **somatotropin** solution for the controlled release of **somatotropin** [Buonomo et al., J. **Animal** Science, 73: 1318-1326, 1995; Klindt et al., J. **Animal** Science, 70: 3721-3733]. In accordance with this method, the concentration of porcine **somatotropin** in blood may be maintained at an effective level for about 6 weeks, and as a result, the feed efficiency is improved and the amount of fat is reduced. However, this miniosmotic pump formulation is expensive and it must be surgically **implanted**.

SUMM Thus, a commercially viable sustained-release formulation has not yet been established, i.e., there continues to exist a need to develop a sustained-release formulation of an **animal** growth hormone.

SUMM Accordingly, it is an object of the present invention to provide a sustained-release formulation of an **animal** growth hormone which is capable of maintaining its effect over 1 week when administered, and a method for the preparation thereof which is free

from the risk of denaturing the hormone and suitable for a mass-production.

SUMM In accordance with the present invention, a solid pellet containing a hormone and an excipient is coated with a film composed of a biodegradable polymer and a poloxamer (surfactant) to obtain a sustained-release formulation of an **animal** growth hormone. Further, there is provided a process for the preparation thereof comprising; tabletting a powder mixture of a hormone and an excipient to obtain solid pellets and coating the pellets with a solution containing a biodegradable polymer and a poloxamer.

DRWD FIG. 1 compares the **somatotropin** dissolution curve of the pellets coated with a polymer film, prepared in accordance with the present invention, with that of uncoated pellets.

DRWD FIG. 2 shows the change in **somatotropin** dissolution from the inventive pellets depending on the constitution of the coating film.

DRWD FIGS. 3a and 3b shows the effects on the weight of dwarf rats of administering various **somatotropin** formulations after storing at 4.degree. C. for 1 week (FIG. 3a) or at 30.degree. C. for 1 month (FIG. 3b).

DETD The formulation of the present invention is produced by coating a solid pellet, comprising an **animal** growth hormone and an excipient, with a film which is capable of regulating the rate of hormone release. The activity of the hormone may be preserved best in a solid formulation and this form is particularly suitable for mass-production wherein a conventional tabletting machine may be used.

DETD The **animal** growth hormone suitable for use in the formulation of the present invention is bovine **somatotropin** or porcine **somatotropin** produced by DNA recombination techniques and the amount thereof may be preferably 20-80 wt % of the total weight of the formulation. The effective daily dosage of porcine **somatotropin** is known to be 100 .mu.g/kg [J. Anim. Sci., 68: 640-651(1990)]. A **pig** weighing over 70 kg requires about 7 mg/day of hormone, or about 100 mg of hormone for a 2 week hormone treatment.

DETD Accordingly, when the hydrophilic drug content is large, the rate of the drug release is influenced not by the excipient, but by the rate of the drug diffusing through the pathways described above. Accordingly, the drug content may become one of the limiting factors in designing a sustained-release formulation. For example, U.S. patent application Ser. No. 4,761,289 discloses a sustained-release formulation comprising 25 to 75 wt % of bovine **somatotropin**. This formulation is prepared in a matrix form by using polymers such as polylactide, polycaprolactone, ethylvinylacetate and the like. However, release profiles of these formulations were not provided.

DETD U.S. patent application Ser. No. 5,342,622 discloses a peptide or protein **implant** coated with a swellable, permeable film made of a non-degradable addition polymer e.g., a copolymer of ethyl acrylate and methyl methacrylate (Eudragit E 30D). This formulation, however, is inferior to the formulation of the present invention, which comprises a coating of a biodegradable condensation polymer, in terms of, e.g., storage stability at 30.degree. C. (see Test Example 3).

DETD In the present invention, a bovine or porcine **somatotropin** powder obtained by a freeze-drying or spray-drying method may be used in an amount of 20-80 wt % based on the total weight of the formulation. The freeze-drying step does not cause denaturation of the protein, but the particles obtained thereby have irregular shapes as well as a wide size distribution. In contrast, spray-dried particles are nearly spherical in shape and show a relative narrow size distribution. However, the spray-drying method gives a maximum yield of only 70-80%. Accordingly, a suitable drying process may be selected based on consideration of the economics and the process variables.

DETD An excipient having a desirable particle size is mixed with an **animal** growth hormone powder in a desired ratio according to a well-known method, e.g., ball-mill. The mixed powder is tabletted to obtain pellets of cylindric shape having a diameter of 2.5-4.5 mm and

length of 2-6 mm. The above pellet size may be suitable for **implantation** using the conventional administering tools for **animals**, i.e., **pigs** and **cows**, without recourse to a surgical operation. However, the exact size and shape of the pellet may vary, depending on the amount of administered drug and other factors.

DETD Step 1) Preparation of a Pellet of Porcine **Somatotropin** by Direct Tabletting Method

DETD 10 g of paraffine wax and 10 g of polyethyleneglycol 35000 (PEG 35K) were passed through a 0.84 mm sieve and mixed with 20 g of freeze-dried recombinant porcine **somatotropin** powder (Korean Patent Application No. 86-11710) using a ball mill (Erveka) for 4 hours. The mixed powder thus obtained was formed into cylinder-shaped pellets having an average diameter of 3 mm and an average length of 6.5 mm by manually operating a tabletting machine (Korsh, EKO). An automatic tabletting operation was also attempted to produce pellets composed of polyethylene-glycol 35,000 (PEG 35K), carnauba wax and porcine **somatotropin** (PST) in a weight ratio of 1:1:2, and each pellet having an average weight, diameter and length of 54.8 mg, 4.0 mm and 4.6 mm, respectively.

DETD A formulation of porcine **somatotropin** was prepared in accordance with the same method in Example 1 except that the ratio of L-PLA to Pluronic F68 was 9:1.

DETD A formulation of porcine **somatotropin** was prepared in accordance with the same method in Example 1 except that the ratio of L-PLA to Pluronic F68 was 7:3.

DETD 1 kg of the fake pellets obtained above and fifty pellets of porcine **somatotropin** obtained in Step 1 of Example 1 were spray-coated with the coating solution prepared above using a Hi-Coater. The rate of fan rotation was 25 rpm; the air pressure was 1.5 kg/cm.sup.2 ; the temperature of the influx air was 30.degree. C.; and the spray rate of the coating solution was controlled at 20 ml/min by using a gear pump. The coated pellets were air dried for 30 min, and then, in a drying oven at below 0.001 torr and room temperature for 12 hours. The pale white pellets containing porcine **somatotropin** were separated from the fake yellow pellets.

DETD A porcine **somatotropin** formulation was produced in accordance with the same procedure in Example 1 using a Eudragit suspension(Eudragit NE30D, Rohm Pharm tech) as a coating solution without dilution.

DETD Test Example 1: Dissolution Test of the Formulation of Porcine **Somatotropin**

DETD To each of two 40 ml glass vials, each containing 15 ml of phosphate buffered saline (pH 7.4), were added the uncoated pellets obtained in Example 1 and the coated pellets obtained in step 2 of Example 1, respectively. The vials were set in a shaker maintained at 37.degree. C. and 100 rpm and 5 ml samples were taken at a fixed interval and each sampling was followed immediately by supplementing 5 ml of buffer solution. Standard porcine **somatotropin** solutions having concentrations of 0.1, 0.2, 0.5 and 1 mg/ml were prepared and their absorbances at 278 nm were measured with a spectrophotometer to obtain a standard calibration curve. The concentration of a sample was then calculated based on its absorbance relative to the standard.

DETD FIG. 1 compares **somatotropin** dissolution curve of the pellets coated with polymer film with that of the uncoated pellets. The % dissolution represents the cumulative amount of the hormone eluted relative to the initial content of the hormone. As shown in FIG. 1, the released rate of the drug was remarkably slow with the coated pellet and the total amount of porcine **somatotropin** released by the coated pellet in 13 days was below 60%, whereas the uncoated pellet released more than 60% in one day. This result shows that the formulation of the present invention is suitable for a sustained-release formulation of porcine **somatotropin**.

DETD Test Example 2: Dissolution Test according to the Constitution of Film on Formulation of Porcine **Somatotropin**

DETD The dissolution tests of the porcine **somatotropin** formulations

obtained in Example 1 to 3 were conducted in accordance with the same procedure as in Test 1. The results in FIG. 2 show that as the poloxamer content of film increases, the dissolution rate increases.

DETD Test Example 3: Effect of Formulation of Porcine **Somatotropin** on Weight Gain of Dwarf Rats and Stability of Formulation

DETD It is well known that an **animal** growth hormone, e.g., bovine **somatotropin** or porcine **somatotropin** brings about weight gain in rats [J. of Anim. Sci., 73:1019-1029, 1995]. Dwarf rats having the heredity of low growth hormone secretion were employed in a test to examine the effect of the porcine **somatotropin** formulation of the present invention.

DETD First, for the purpose of evaluating the storage stability concurrently with the activity test, the coated formulations obtained in Example 4 and Comparative Example, and the uncoated formulation obtained in Step 1 of Example 1 were stored at 4.degree. C. for 1 week in one case, and 30.degree. C. for 1 month in the other. Identifying labels were attached to the tails of 8 weeks-old female dwarf rats, weighed for 3 days and those deviating far from the average weight were excluded so that a group of rats having a uniform weight distribution could be. After fixing the forefeet, hindfeet and the foreteeth of a rat, a 1 cm cut was made on the ventromedian line, a pellet was inserted into the hypoderm, and the incision was closed using a silk suture in accordance with a discontinuous suture method. After the **implantation**, they were weighed every day at a fixed time and compared with rats in a control group.

CLM What is claimed is:

1. A sustained-release formulation of an **animal** growth hormone comprising a solid pellet containing an **animal** growth hormone and an excipient; and a film composed of a biodegradable polymer and a poloxamer, wherein said film coats said pellet, and wherein the biodegradable polymer is polylactide (PLA), polyglycolide (PGA), poly(lactide-co-glycolide) (PLGA) or a mixture thereof.

2. The formulation of claim 1, wherein the **animal** growth hormone is bovine **somatotropin** or porcine **somatotropin**

.

3. The formulation of claim 1, wherein the amount of the **animal** growth hormone is 20-80 wt % based on the total weight of the formulation.

8. A process for the preparation of a sustained-release formulation of an **animal** growth hormone, which comprises; directly tabletting a powder mixture of an **animal** growth hormone and an excipient to obtain a solid pellet; coating the pellet with a film composed of a biodegradable polymer and a poloxamer.

9. The process of claim 8, wherein the **animal** growth hormone is spray-dried.

10. The process of claim 8, wherein the **animal** growth hormone is freeze-dried.

IT 9000-69-5, Pectin 9004-34-6, Cellulose, biological studies 9004-54-0, Dextran, biological studies 9005-32-7, Alginic acid 9010-88-2, Eudragit ne30d 25322-68-3 26009-03-0, Polyglycolide 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26161-42-2 26202-08-4, Polyglycolide 26680-10-4, Polylactide **26780-50-7**, Glycolide-lactide copolymer 33135-50-1, Poly(L-lactide) 66419-50-9, Bovine somatotropin 106392-12-5, Poloxamer. 126467-48-9, Porcine somatotropin
(sustained-release pharmaceutical pellets contg. animal growth hormones)

L139 ANSWER 3 OF 5 USPATFULL
AN 89:85763 USPATFULL

TI Multi-component long-acting medicament formulation for **implantation**
IN Deasy, Patrick B., Dublin, Ireland
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 4874612 19891017
AI US 1988-152004 19880203 (7)
PRAI DE 1987-3704275 19870212
DE 1987-3710175 19870327
DT Utility
EXNAM Primary Examiner: Swisher, Nancy A. B.
LREP Finnegan, Henderson, Farabow, Garrett and Dunner
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 339
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Multi-component **implants** which contain at least two shaped pieces containing active compound, wherein these shaped pieces contain biologically degradable copolymers of lactic acid and glycolic acid with a ratio by weight of lactide to glycolide of 90:10 to 60:40, and wherein there are at least two types of shaped pieces, A and B, type A containing copolymers with a content of lactide which is 5 to 15% by weight lower than in type B, release the active compound over a prolonged period, uniformly or with increasing amount released.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Multi-component long-acting medicament formulation for **implantation**
AB Multi-component **implants** which contain at least two shaped pieces containing active compound, wherein these shaped pieces contain biologically degradable copolymers of lactic acid and glycolic acid with a ratio by weight of lactide to glycolide of 90:10 to 60:40, and wherein there are at least two types of shaped pieces, A and B, type A containing copolymers with a content of lactide which is 5 to 15% by weight lower than in type B, release the active compound over a prolonged period, uniformly or with increasing amount released.
SUMM The invention relates to a multi-component long-acting medicament formulation for **implantation**, which contains biologically degradable shaped pieces containing active compound and shaped pieces containing no active compound.

SUMM Pharmaceutical formulations in the form of particles or pellets with controlled release of active compound in which the active compound is present in an intimate mixture with a solid polylactide or another biologically degradable polyester and which are suitable for **implantation** are already known from British Pat. No. 1,325,209. It is furthermore known, for example from European Patent No. A-25,698, that copolymers of lactic acid and glycolic acid can be used for the preparation of such formulations. The polyesters are slowly degraded and thereby release the active compound over a correspondingly long period of time.

SUMM Although medicament formulations of this type are tolerated well, they have the disadvantage that they cannot guarantee uniform and increasing release of the active compound, especially in the event of treatment periods lasting a long time. Rather, the active compound dispersed in the matrix is released in continuously decreasing amounts as a result of the ever decreasing surface due to the gradual degradation of the **implant**.

SUMM Attempts have therefore already been made to achieve a more uniform release of active compound by different distribution of the active compound in the pellet or by admixing additives which can easily be dissolved out. Attempts have also been made to achieve this aim by particular geometric designs of the **implant**, for example by

forming the **implant** as a thin film or as a hollow fiber. It has been found here, however, that biologically degradable aliphatic polyesters are, even after addition of plasticizers, still so brittle that thin films and hollow fibers are unsuitable for the production of **implants** which are to be deposited underneath the skin by means of an **injection** needle with a wide-bore cannula. Such shapes of **implants** require the use of biologically non-degradable elastomers, such as silicone rubber, if they are not to break even during **implantation** or immediately after being deposited under the skin.

SUMM The invention relates to a multi-component **implant** which contains at least two shaped pieces containing active compound, wherein these shaped pieces contain biologically degradable copolymers of lactic acid and glycolic acid with a ratio by weight of lactide to glycolide of 90:10 to 60:40, and wherein there are at least two types of shaped pieces, A and B, type A containing copolymers with a content of lactide which is 5 to 15% by weight lower than in type B.

SUMM Such a combination of types of shaped pieces means that the rate of release of the active compound can be controlled in an optimum manner with uniform or increasing release of the active compound over a prolonged period (up to 12 months), and the disadvantages of the known **implants** are thus overcome. Furthermore, the **implant** has the advantage that a so-called burst effect, in which a large amount of active compound is released at the start, is minimied.

SUMM The **implant** can contain up to 20 shaped pieces containing active compound, in particular 5 to 15 shaped pieces, in particular an odd number of shaped pieces, which are combined in an arrangement in the form of a chain or sandwichlike. It preferably contains 1 to 7 shaped pieces of type B and 2 shaped pieces of type A, there being a shaped piece A located at each of the two ends of the chain.

SUMM The shaped pieces required for the medicament formulation according to the invention are in general in the shape of a cylinder with a diameter of 2 to 6 mm, preferably 3 to 4 mm, and a thickness (=height) of 1 to 6 mm, preferably 2 to 4 mm. The total length of the **implant** can preferably vary between 1 and 4 cm. The shaped pieces are preferably prepared by a procedure in which a mixture containing the active compound, the biologically degradable polymer or copolymer and other suitable additives, such as lubricants, is punched between the flat dies of a tableting press.

SUMM The release of active compound from the shaped pieces of the **implant** can be considerably influenced by various parameters. An increase in the molecular weight of the polyester delays its degradation and the release of the active compound. Within polymers and copolymers of polylactic acid and polyglycolic acid, the rate of degradation increases from poly-L-lactic acid via poly-DL-lactic acid and polylactic/glycolic acid up to polyglycolic acid, at the same molecular weight. An increase in the amount of active compound in the shaped piece increases the rate of release, as does the addition of plasticizers or additives which can easily be dissolved out. The release of active compound can likewise be accelerated by increasing the number of shaped pieces or increasing their surface area. On the other hand, an increase in the pressing pressure or a treatment of the pressed tablets by applying increased temperatures has an inhibiting effect on the release of the active compound.

SUMM It is possible by carefully matching the composition of the shaped pieces containing active compound to control the release behavior of the active compound **implants** in such a way that the duration of release can be varied depending on the nature of the active compound.

SUMM In a further embodiment of the invention, it is possible for the

implants according to the invention to contain shaped pieces which are of type C, contain no active compound and can be inserted between the shaped pieces containing active compound described above. These shaped pieces can be used to improve the release behavior of the **implant** over a prolonged period. The shaped pieces of type C are expediently composed of the same copolymers as described for shaped pieces A and B containing active compound.

SUMM The **implants** according to the invention can be used, in particular, in **veterinary** medicine, but are also suitable for use in human medicine when it is neessary to guarantee a uniform or increasing concentration of medicament in the organism over a prolonged period of time. Such long-acting **implants** are suitable, in particular, for hormonal disorders, for cancer treatment, for the treatment of infections, circulatory disorders and mental handicaps, and for birth control.

SUMM In **veterinary** medicine, such **implants** can be used for the treatment of deficiency states (vitamin and trace element deficiencies), chronic infections (long-term administration of anti-infective agents), ecto- and endoparasitoses and impaired function or faulty regulation of endocrine organs (hormone replacement), as well as for uniform release of substances or hormones, especially those which influence growth.

SUMM Natural hormones, such as 17 .beta.-**estradiol** and/or **testosterone** or their esters, as well as synthetic hormones, such as **trenbolone acetate** or resorcylic acid lactone (**zeranol**), significantly influence the growth of **calves** if they are administered in the form of the multi-component **implant** according to the invention. Since the **implant** can release the active compound over a period of 3 to 12 months, depending on the properties of the shaped pieces selected for this, only a single **implantation** is necessary for each **animal**, in contrast with the known **implants**.

SUMM The following active compounds can preferably be employed: steroids or other substances with an anabolic effect, such as **trenbolone**, **zeranol**, 17 .beta.-**estradiol**, **testosterone**, **progesterone** or combinations thereof, peptide hormones or substances which release peptide hormones, such as **somatotropin** , **somatotropin**-releasing hormone or gonadotropin-releasing hormone.

SUMM The finished **implants** are deposited directly underneath the skin with the aid of a commercially available **implantation** unit.

DETD For the shaped pieces containing active compound, 180 mg of 17 .beta.-**estradiol** were mixed with 120 mg of 80/20 lactide/glycolide copolymer and dissolved in acetone. The solvent was then removed by distillation in vacuo. Tablets were manufactured from the resulting material using a tableting press. The shaped pieces containing no active compound were manufactured analogously.

DETD **Implant** I

DETD The **implant** was composed of 5 shaped pieces in the form of cylindrical tablets containing active compound: 3 tablets had a higher content of active compound (type B) and had a diameter of 4 mm and a thickness of 2 mm. The other 2 tablets had the same dimensions but a lower lactide content (type A) and were combined with the tablets of type B in an arrangement in the form of a chain in the sequence: ABBBA.

DETD The tablets B had a copolymer content of 40% by weight with a lactide/glycolide ratio of 80/20 and a content of 17 .beta.-**estradiol** active compound of 60% by weight. The tablets A were composed of 50% by weight of polymers with a lactide/glycolide ratio of 70/30, and of 50% by weight of 17 .beta.-**estradiol**.

DETD **Implant** II

DETD The **implant** was composed of 9 shaped pieces in the form of cylindrical tablets. Compared with **implant** I, **implant** II contained an additional 4 shaped pieces containing no active compound (type C) of the same dimensions as the tablets A or B. The tablets C were inserted between the tablets A and B containing active compound in the following sequence: A-C-B-C-B-C-B-C-A.

DETD The rate of release of 17 .beta.-**estradiol** from the **implants** I and II described above was determined by determining the blood plasma level before, during and after **implantation** to castrated male **cattle**. In addition, the effect on the weight gain was examined by determination of the body weight of the **animals** before, during and after the **implantation**.

DETD 13 bullocks were divided into 3 groups: two groups of 5 **animals** each (group I and II) and one group of 3 **animals** (group III).

DETD Group I (mean weight 145.2 kg) received **implant** I

DETD Group II (mean weight 144.8 kg) received **implant** II

DETD Group III (mean weight 141.3 kg) received no **implant**=control

DETD The **implantation** was carried out using a commercially available applicator. The **implant** was inserted in the dorsal side of the external ear of the **animals**.

DETD 42 days after the **implantation**, the **implants** were removed from two **animals** from Group I and II, and the **estradiol** content remaining in the **implant** was determined by HPLC analysis. 84 days after the **implantation**, the **implants** were removed from the remaining 3 **animals** in each group I and II, and were analyzed.

DETD At defined times before, during and after the **implantation** blood samples were taken from the tested **animals** in order to establish the plasma level of **estradiol**. The **estradiol** content was determined by a radioimmunological method.

DETD In addition, the experimental **animals** were weighed at intervals of 2 weeks after the **implantation** in order to determine the weight gain.

DETD A defined amount of feed was measured out for each **animal** at each feeding during the experiment, and the intake was monitored.

DETD The amount of **estradiol** released for **implants** I and II after 42 and 84 days is shown in Table 1. The plasma level of **estradiol** is shown in Table 2. The weight gain of the **animals** is evident from Table 3.

DETD It is clearly evident from the results in Tables 1 to 3 that **implants** I and II ensure a proportionate release of **estradiol** over a period of at least 12 weeks, and the weight gain is higher than for the controls.

DETD TABLE 1

Release of 17.beta.-**estradiol** (17.beta.-E) 17.beta.-E content (mg) per **implant**	17.beta.-E content before implantation	17.beta.-E content after 42 days	Release of 17.beta.-E mg/day for 84 days	Release of 17.beta.-E mg/day for 42 days	Release of 17.beta.-E mg/day for 84 days
Implant					
Group I					
78.80/77.06					
	72.0/64.0		0.16/0.31		
76.29/76.63/ 75.55		41.4/35.6/ 45.6		0.42/0.49/ 0.39	
Group II					
77.94/79.09					

68.5/54.0 0.22/0.60
79.23/79.47/ 45.1/49.9 0.41/0.35/
77.96 48.3 0.35

DETD TABLE 2

Estradiol plasma levels

	Days	Group I (pg/ml)	Group II (pg/ml)	Group III (pg/ml)
		(n = 5)	(n = 5)	(n = 3)
	-5	--	11.7	15.8
	-4	14.9	16.5	21.0
Implant	0	21.0	31.0	32.3
administration				
	1	92.6	83.5	16.0
	2	36.0	42.6	20.7
	7	69.5	50.8	20.1
	14	36.6	62.6	21.1
	21	44.8	35.0	13.4
	29	21.5	25.0	23.0
	35	22.5	12.9	10.4
	42	19.5	30.9	23.0
		(n = 3)	(n = 3)	
	49	25.4	32.2	22.3
	56	24.0	21.0	--
	63	38.0	58.3	27.7
	70	53.7	46.0	18.3
	77	68.7	58.3	25.3
Implant	84	160.0	125.0	26.3
removal	85	180.0	130.0	--
	86	110.0	93.3	--
	90	69.0	30.0	31.3

The values relate to pg/ml of plasma and are mean values (X)
n = number of **animals**

DETD TABLE 3

Change in weight (kg) after the **implantation**

Group	0-2	0-4	0-6	0-8	0-10	0-12 week
I	21.4	44.2	62.3	80.0	99.3	113.3
II	21.4	45.0	57.6	69.9	85.6	105.6
III	18.3	35.0	43.3	59.0	70.3	81.3
Control						

CLM What is claimed is:

1. A multi-component long-acting **implant** which contains at least two shaped pieces containing active compound, wherein these shaped pieces contain biologically degradable copolymers of lactic acid and glycolic acid with a ratio by weight of lactide to glycolide of 90:10 to 60:40, and wherein there are at least two types of shaped pieces, A and B, type A containing copolymers with a content olactide which is 5 to 15% by weight lower than in type B.

2. An **implant** as claimed in claim 1, which contains up to 20 shaped pieces.

3. An **implant** as claimed in claim 1, which contains an odd number of shaped pieces.

4. An **implant** as claimed in claim 1, wherein the shaped pieces are arranged in the form of a chain.

5. An **implant** as claimed in claim 4, wherein a shaped piece of type A is located at both ends of the chain.

6. An **implant** as claimed in claim 1, which additionally has shaped pieces which contain no active compound and contain copolymers of lactic acid and glycolic acid as claimed in claim 1.

7. An **implant** as claimed in claim 6, wherein the shaped pieces are arranged in alternating sequence.

8. An **implant** as claimed in claim 1, wherein the active compound content in the shaped pieces A and B varies between 20 and 80 by weight.

9. An **implant** as claimed in claim 1, wherein the active compound content in shaped piece A is 5 to 15% by weight lower than in shaped piece B.

10. An **implant** as claimed in claim 1, which contains an acive compound for human or **veterinary** medical purposes.

11. An **implant** as claimed in claim 1, which contains as active compound a natural or synthetic hormone for **animals**.

12. An **implant** as claimed in claim 1, wherein the average molecular weight of the copolymers is between 10,000 and 30,000, and the polydispersity of the copolymers is between 1.5 and 2.5.

13. An **implant** as claimed in claim 1, wherein each of the shaped pieces are in the shape of a cylinder with a diameter of 2 to 6 mm and a thickness of 1 to 6 mm.

14. An **implant** as claimed in claim 1, wherein the total length of the **implant** is between 1 and 4 cm.

15. An **implant** as claimed in claim 1, wherein up to 20 shaped pieces containing active compound are combined in an arrangement in the form of a chain or sandwich-like.

16. An **implant** as claimed in claim 15, wherein 5 to 15 shaped pieces containing active compound are combined.

17. An **implant** as claimed in claim 1, wherein 1 to 7 shaped pieces of type B and 2 shaped pieces of type A are combined in a chain, the shaped pieces A located at the two ends of the chain.

18. An **implant** as claimed in claim 1, wherein 1 to 7 shaped pieces of type B, 2 shaped pieces of type A and shaped pieces which contain no active compound are arranged in alternating sequence in the form of a chain, the shaped pieces A located at the two ends of the chain.

IT **Veterinary medicine**
(implantable sustained-release pharmaceutical formulations for)
IT **34346-01-5 54512-07-1**, Glycolic acid-L-lactic acid copolymer
(pharmaceutical sustained-release implants contg., as matrix)
IT **50-28-2**, Estra-1,3,5(10)-triene-3,17-diol (17.beta.)-, biological studies
(sustained-release implants contg.)

L139 ANSWER 4 OF 5 USPATFULL
AN 88:75679 USPATFULL
TI Cylindrical **implants** for the controlled release of **growth hormones**
IN Janski, Alvin M., Terre Haute, IN, United States

Yang, Ren-Der, Terre Haute, IN, United States
PA International Minerals & Chemical Corp., Terre Haute, IN, United States (U.S. corporation)
PI US 4786501 19881122
AI US 1985-755093 19850715 (6)
DT Utility
EXNAM Primary Examiner: Schain, Howard E.; Assistant Examiner: Draper, Garnette D.
LREP Guffey, Wendell R.; Farquer, Thomas L.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 491
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method for purifying and concentrating biologically active growth hormone to produce growth hormone in a form suitable for incorporation into a controlled release device (or system). A buffered solution of purified recombinant growth hormone is dialyzed against a buffered solution until the salt level is reduced to less than 5% and then lyophilized.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Cylindrical **implants** for the controlled release of **growth hormones**

SUMM The present invention relates to a method of producing controlled release **implants** adapted for the administration of bioactive recombinant growth hormones at a controlled and continuous rate to a host. More particularly, the invention relates to a method of purifying bovine growth hormone and porcine growth hormone produced by DNA technology in a form suitable for use in controlled release devices.

SUMM Bovine growth hormone (BGH) and porcine growth hormone (PGH) are proteins containing 191 amino acid residues. These proteins are synthesized in the anterior pituitary gland as "pre-growth hormones" having 26 additional amino acid residues attached at the amino terminal end. These 26-amino acid residue sequences are cleaved off prior to secretion from the pituitary cells, yielding the mature hormones. Field trials using BGH purified from pituitary glands demonstrated increased milk production and improved feed-to-milk conversion in **cows** to which the hormone was administered (Machlin, L. J., Journal of Dairy Science, 56:575-580 [1973]). The potential economic value of this hormone sparked interest in obtaining BGH in commercial quantities at reasonable cost. Field trials of native PGH have shown increased growth rates in young **swine** receiving the hormone.

SUMM Administration of BGH to **cattle** and PGH to **swine** has hitherto been only marginally successful. Methods of delivery of drugs that are well known in the art include oral, nasal, rectal, topical, and parenteral **injection** routes of administration. However, it is inconvenient to administer drugs to **cattle** and **swine** by these methods because of the large expense and amount of time required to deliver the drug to each member of a large group of **animals** on a daily basis.

SUMM Subcutaneous **implants** provide an alternative means for administering sustained, effective dosages of recombinant BGH and PGH to each **animal**. The **implant** contains a hormone reservoir surrounded by a protective wall permeable to the hormone. The advantage of these delivery systems is that they provide for controlled and predictable release rates of the hormones to the **animals** over an extended period of time. Unfortunately, we have found that controlled release devices containing BGH and PGH produced by recombinant microorganisms in fermentation media are subject to swelling and partial disintegration after **implantation**. This phenomenon dilutes the hormone in the **implant** and adversely affects the rate of release of the hormone. Therefore, the commercial need for a

method of producing recombinant growth hormones in a form capable of effectively being incorporated into a controlled release **implant** persists.

SUMM The present invention relates to improved **implants** for the controlled and continuous administration of growth hormones to host **animals**. The **implants** are made of a compressed composition containing a growth-promoting amount of an **animal** growth hormone produced by recombinant DNA technology. More particularly, the present invention relates to a method of purifying and concentrating bovine growth hormone and porcine growth hormone produced by recombinant DNA technology in a form suitable for use in controlled release **implants**. A method of producing controlled release **implants** for administration of growth hormones into **animals** is also disclosed. The method of the invention is based on our discovery that reduction of the salt level of the growth hormones to less than 5% by weight eliminates the swelling problem previously encountered when recombinant growth hormones were incorporated into controlled-release **implants**. Unlike native growth hormone, the recombinant product contains a substantial amount of salt which is present largely as a result of salts in buffers used in the recovery operations.

SUMM In addition to removal of most of the salt, the present invention relates to a method for producing recombinant growth hormones in the presence of buffer salts that will result in a physiological pH of about 7.4 within the **implant** upon wetting in a physiological environment. This aspect of the invention prevents a pH gradient between the **implant** and its in vivo environment from developing. Such a gradient would cause uncontrolled release of growth hormone.

SUMM In accordance with the method of the invention, the **animal** growth hormone, which is recovered from transformant microorganisms in a fermentation medium, is dialyzed against a dialysis buffer having a pH from basic to physiological pH until the amount of salt present in the growth hormone is less than 5%. Methods other than dialysis for salt removal may provide for preparation of a low-salt product, e.g., size exclusion chromatography. The low-salt growth hormone thus produced is lyophilized and then admixed with a biocompatible polymer to produce a composition which can be compressed into a unitary dosage form capable of being subcutaneously **implanted**. The term "physiological pH" refers to a pH of about 7.4.

DRWD The single FIGURE is a cross-sectional representation of a cylindrical **implant** for the controlled-release administration of growth hormone to an **animal**.

DETD We have developed a new method of producing growth hormones suitable for controlled release **implants** for administration to **animals**. More particularly, the invention provides a method of removing salts and concentrating bovine growth hormone or porcine growth hormone produced by recombinant DNA technology which results in a composition suitable for use in a controlled release **implant** for subcutaneous **implantation**. As used herein, the terms "bovine growth hormone", "BGH", "porcine growth hormone", and "PGH" include fragments of the hormones which may, for example, have varying portions of the amino terminal ends of the hormones deleted, or may have various substitutions or modifications in the BGH and PGH sequences which do not destroy the biological activity of the polypeptides. BGH and PGH polypeptides lacking various portions of the amino terminal end of the hormones have been shown to retain biological activity.

DETD Either the lyophilized BGH or PGH may be incorporated in an **implant** for subcutaneous administration as described in the following paragraphs.

DETD For the controlled administration of growth hormone (GH) from solid **implants**, it is advantageous to have a matrix consisting of the GH, a polymer as a filler and other suitable additives. It is important

that the polymeric filler be biocompatible and compatible with the GH. For example, if the polymer is too hydrophobic, it may bind the GH so strongly that the protein may not be released readily. In extreme cases, the GH may even be denatured by the hydrophobic matrix and thus rendered inactive. On the other hand, if the polymer is too hydrophilic, penetration of water into the **implant** can be rapid. The wet **implant** may facilitate aggregation of the GH which can result in decreased solubility and/or bioactivity. Thus, the ideal polymeric filler should exhibit a balance between the hydrophobic and hydrophilic forces.

DETD Ethyl cellulose (EC) is a commercially available, water-insoluble polymer which fits the requirements of a polymeric filler for an **implant** containing GH. It is a derivative of cellulose in which the hydroxyl groups have been partially etherified. The ether groups provide the hydrophobicity while the hydroxyl groups give hydrophilicity to the polymer. By altering the degree of etherification, one can achieve the desired balance between the two types of interaction. Another advantage of EC is the presence of the unsubstituted hydroxyl groups which may stabilize the GH in the wet **implant** and minimize aggregation of the protein. A third advantage is the ability of EC to act as binder in tablet preparations. By controlling the amount of the EC in the matrix, it is possible to control the compactness of the solid pellet. This can be used to control the water penetration into the **implant** and the disintegration of the pellet.

DETD GH, being a delicate protein, may easily be denatured when brought into contact with organic solvents. In conventional tablet formulations, the drug is usually mixed with a solution of the polymeric filler, dried and granulated. This may not be desirable for the formulation of GH as a solid **implant**. EC offers another advantage in that it can be formulated in the dry state with the GH, thus avoiding the potentially damaging exposure to organic solvents.

DETD In summary, EC can be very useful in the formulation of a solid **implant** containing GH. The amount of EC can vary from 10 to 50% depending on the type of release profile needed. It can also be used in conjunction with other suitable additives such as sucrose, lactose, magnesium stearate, etc. which are employed in conventional tablet formulation for various purposes.

DETD Referring to the single Figure, a typical controlled release **implant** incorporating BGH can be produced as follows. BGH (75 parts; particle size: 150-250 microns) and EC (25 parts; particle size: 150-250 microns) are mixed in a vial using a vortex shaker. The matrix is then pelleted with a Stoke's machine to give cylindrical pellets weighing 50 mg and measuring 4.0 mm in diameter and 3.9 mm in length. The pellets are placed in microporous polyethylene (MPE) tubes and the ends of the tubes sealed with non-porous polyethylene film. The resultant cylindrical **implant** for the controlled release of GH is illustrated in cross-section in the single Figure. The cylindrical **implant** contains a central core pellet 10 which is surrounded along the length of the cylinder by a releasing surface 12 of the microporous polyethylene film. At the end or the cylinder are nonreleasing surfaces 14 of non-porous polyethylene.

DETD Upon subcutaneous **implantation** in **cattle**, the releasing surface 12 of MPE acts as a barrier to slow the rate of diffusion of BGH out of the **implant**, thereby resulting in a prolonged release of the hormone. If desired, other microporous polymer films may be used in place of the MPE. These include, for example, microporous films of ethyl celluIose, polycaprolactone and polymethyl methacrylate. The non-releasing surface 14 of non-porous polyethylene (or other non-porous polymer) serves to prevent BGH from being released through the ends of the **implant**.

DETD When an **implant** of PGH in the presence of pH 7.4 buffer salts is wetted by body fluids at about pH 7.4, little or no pH gradient should exist, allowing for a more predictable release rate of PGH from the **implant**.

DETD A formuation for the preparation of growth hormone **implants** is prepared from the following ingredients:

CLM What is claimed is:

1. A cylindrical **implant** for the controlled and continuous administration of growth hormone to a host comprising a compressed composition of an **animal** growth hormone produced by expression of a gene coding for the hormone in a transformant microorganism, said growth hormone being recovered from said microorganism and processed to produce a growth hormone containing less than 5% salt, and a biocompatible and growth hormone compatible polymer, said composition being surrounded along the length of the cylinder by a microporous polymer film and sealed at its ends by a non-porous polymer film.

2. The **implant** of claim 1 wherein the growth hormone is selected from bovine growth hormone and porcine growth hormone.

3. The **implant** of claim 2 wherein the compatible polymer is ethyl cellulose.

4. The **implant** of claim 2 wherein the compressed compostion contains about 30 weight percent growth hormone, 30 weight percent ethyl cellulose and 40 weight percent sucrose.

5. The **implant** of claim 2 wherein the microporous polymer is microporous polyethylene and the non-porous polymer is non-porous polyethylene.

6. The **implant** of claim 1 wherein the compressed composition contains from about 50-90 weight percent growth hormone and from about 10-50 weight percent biocompatible and growth hormone compatible polymer.

7. The **implant** of claim 6 wherein the biocompatible and growth hormone compatible polymer is ethylcellulose, the microporous polymer is microporous polyethylene and the non-porous polymer is non-porous polyethylene.

IT **Cattle**
IT **Swine**
(recombinant growth hormone of, in controlled-release implant, salt content in relation to)
IT 57-50-1, Sucrose, biological studies **9004-57-3**, Ethyl cellulose
(in controlled-release implant contg. recombinant growth hormone of cattle or swine, salt content in relation to)
IT **9002-72-6**, Somatotropin
(recombinant, of cattle and swine, in controlled-release implant, salt content in relation to)

L139 ANSWER 5 OF 5 USPATFULL
AN 88:24123 USPATFULL
TI **Veterinary implant**
IN Seamark, Robert F., Beulah Park, Australia
Kennaway, David J., Prospect, Australia
Dunstan, Eugene, Naracoorte, Australia
PA Gene Link Australia Limited, South Melbourne, Australia (non-U.S. corporation)
PI US 4738679 19880419
WO 8503227 19850801
AI US 1985-783954 19850926 (6)
WO 1985-AU13 19850126
19851015 PCT 371 date
19851015 PCT 102(e) date
PRAI AU 1984-3361 19840126
DT Utility
EXNAM Primary Examiner: Apley, Richard J.; Assistant Examiner: Cannon, Alan W.
LREP Merchant, Gould, Smith, Edell, Welter & Schmidt
CLMN Number of Claims: 9
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 476
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of regulating the reproductive functions of **animals**, preferably domesticated **ruminants**, and **veterinary implants** for use in such a method are provided. The **veterinary implant** tablet comprises about 2-15% by weight of a fatty acid salt compression binder, about 25-50% by weight of a directly compressible vehicle selected from the group consisting of calcium phosphate and derivatives thereof, about 1-5% by weight of a granulating agent, and an amount of melatonin effective to maintain blood melatonin at, or above, a natural nighttime level of an **animal** to be treated for a period of time effective to accelerate an onset of breeding activity in mature **animals** or to delay an onset of puberty in prepubescent **animals**. The **implant** tablet provides a substantially continuous release rate of melatonin so as to maintain blood melatonin at, or above, the stated level. A method for preparing such a **veterinary implant** tablet is also described. A method of modifying the seasonal breeding activity of **animals** is also provided which comprises administering to an **animal** to be treated the disclosed **veterinary implant** tablet.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Veterinary implant**
AB A method of regulating the reproductive functions of **animals**, preferably domesticated **ruminants**, and **veterinary implants** for use in such a method are provided. The **veterinary implant** tablet comprises about 2-15% by weight of a fatty acid salt compression binder, about 25-50% by weight of a directly compressible vehicle selected from the group consisting of calcium phosphate and derivatives thereof, about 1-5% by weight of a granulating agent, and an amount of melatonin effective to maintain blood melatonin at, or above, a natural nighttime level of an **animal** to be treated for a period of time effective to accelerate an onset of breeding activity in mature **animals** or to delay an onset of puberty in prepubescent **animals**. The **implant** tablet provides a substantially continuous release rate of melatonin so as to maintain blood melatonin at, or above, the stated level. A method for preparing such a **veterinary implant** tablet is also described. A method of modifying the seasonal breeding activity of **animals** is also provided which comprises administering to an **animal** to be treated the disclosed **veterinary implant** tablet.
SUMM This invention relates to a method of regulating the reproductive functions of **animals**, particularly domesticated **ruminants**, and to **veterinary implants** for use in such a method.

SUMM In our earlier Australian patent application No. 78305/81 there is described a method of artificially mimicking changing photoperiod and thus the seasonal breeding activity of **sheep** and goats by the judicious feeding of melatonin or other related indoles or indole derivatives.

SUMM The role of seasonal environmental factors, in particular the photoperiod, in determining the breeding period of **sheep** is well established. Under natural conditions the shortening of day length as summer leads to autumn is the main trigger to the reproductive system to commence ovarian cyclicity. Our previous application shows that melatonin treatment can mimick the effects of short day length on ewes, such that the breeding season is advanced and basal prolactin levels are depressed.

SUMM In the earlier patent specification this was achieved by feeding the **animal** with food containing melatonin or related indole or

indole derivatives for a period of time sufficient for the **animal** to commence cyclic ovarian activity. This was achieved by absorbing the melatonin in food pellets, and in this way 2 mg of melatonin per day was fed to each **animal**.

SUMM This however requires the daily feeding of the pellets to the **animals** for a period of three to six weeks.

SUMM Accordingly, in a first aspect, the present invention provides a **veterinary implant** including an effective amount of

SUMM (b) a **veterinarily** acceptable carrier or excipient selected to provide, in use, in combination with the active ingredient (a), a generally continuous release rate of active ingredient sufficient to maintain blood melatonin, or its equivalent, at, or above, natural night time level. For domesticated **ruminants** such as **sheep** and goats this level is approximately 100 pg/ml. Preferably the **veterinary implant** according to the present invention is formed by compression.

SUMM In a further aspect the present invention provides a method of modifying the seasonal breeding activity of **animals** which method includes inserting a **veterinary implant** of the type described herein into an **animal** to be treated.

SUMM The modification of breeding activity may be such as to accelerate the onset of breeding activity or delay the onset of puberty. In delaying the onset of puberty the onset of the breeding season of the **animal** may be altered. This effect may continue for an extensive period e.g. 2-4 years.

SUMM By the term "melatonin" as used herein, we mean the active ingredient in the **veterinary implant** selected from melatonin, related indoles and derivatives thereof or mixtures thereof.

SUMM In the following description reference will be made to the ethicacy of the **veterinary implants** in **sheep**, goats and **cattle**. It should be understood, however, that such **animals** are mentioned for illustrative purposes only and the **veterinary implant** is applicable to **animals** generally. The **veterinary implant** may be applied to **animals** including **sheep**, goats, **horses**, **cattle**, deer, buffalo, **pigs**, ferrets, mink, fox, sable, ermine, bear, camels, lamas and the like. The **veterinary implants** may further be applied to the regulation of seasonal breeding activity in birds, reptiles, including alligators, crocodiles, turtles and snakes, and fish including sturgeon, trout, salmon and eels.

SUMM As discussed below, initial experiments exploring the effects of continuous melatonin administration were carried out utilizing **implants** in the form of melatonin filled silastic sachets. Whilst these **implants** were useful for experimental purposes, such **implants** are deficient in a number of aspects. Firstly, they are difficult and therefore expensive to manufacture and are therefore impractical for large scale application. Further, their size makes their introduction into an **animal** and subsequent removal a difficult surgical technique. It would be a significant advance in the art if a **veterinary implant** could be provided which overcomes, or at least alleviates, some of these difficulties.

SUMM In a preferred aspect the present invention provides a **veterinary implant** as described above, further including

SUMM The lubricant may be present in an amount of approximately 1 to 30% by weight, preferably 1 to 5% by weight based on the total weight of the

veterinary implant. The lubricant may be a food grade lubricant. The lubricant may be a natural food source lubricant. The lubricant may be derived from vegetable oil. The lubricant may be a lubricant of the type sold under the trade designation "LUBRITRAB" and available from Edward Mendell Co. Inc., New York, U.S.A.

SUMM According to a still further aspect of the present invention the **veterinary implant** may further include

SUMM The binder may be present in amounts of from approximately 1 to 30% by weight based on the total weight of the **veterinary implant**. The binder may be present preferably in amounts of approximately 2 to 15% by weight.

SUMM As stated above, the **veterinary implant** according to the present invention in a preferred aspect may be formed by compression. The active ingredient (a) and the **veterinarily** acceptable carrier (b) may be intimately mixed and then compressed. The **veterinary implants** may be compressed in a tablet press.

SUMM In a preferred form the present provides a **veterinary implant** wherein the **implant** is formed by direct compression. In this form the **veterinarily** acceptable carrier or excipient may include approximately 25 to 50% by weight based on the total weight of the **veterinary implant** of a directly compressible vehicle selected to control the release rate of active ingredient. The directly compressible vehicle may be an acid salt. The acid salt may be a phosphate salt. The directly compressible vehicle may be an alkaline earth metal salt. A calcium phosphate is preferred. An hydrated acid salt may be used. A dibasic calcium phosphate dihydrate is preferred. The acid salt may be a calcium phosphate of the type sold under the trade designation "ENCOMPRESS" and available from Edward Mendell Co. Inc., New York, U.S.A.

SUMM The acid salt is preferably present in an amount of from approximately 30 to 40% by weight based on the total weight of the **veterinary implant**.

SUMM Accordingly, in a further aspect of the present invention there is provided a **veterinary implant** of the type described above wherein the **implant** is formed utilizing a granulation and compression method. In this form, the **veterinarily** acceptable carrier (b) includes an effective amount of a granulation agent selected from a compound or a high molecular weight compound or mixtures thereof.

SUMM The granulating agent may be present in amounts of from approximately 1 to 30% by weight preferably 1 to 5% by weight based on the total weight of the **veterinary implant**. The granulating agent may be selected from a cellulose compound or other high molecular weight compound or mixtures thereof. The cellulose compound or high molecular weight compound may be a water insoluble compound. The cellulose compound may be selected from ethyl cellulose, methyl cellulose, cellulose acetate or derivatives thereof. Cellulose acetate phthalate or a compound sold under the trade designation "METHOCEL" may be used. As the high molecular weight compound, vinyl polymer may be used. Polyvinyl pyrrolidone is preferred. Alternatively, or in addition, naturally occurring high molecular weight compounds, such as the waxes, for example beeswax, may be included.

SUMM The polyvinyl pyrrolidone utilized in the **veterinary implants** according to the present invention may be selected from a range of polyvinyl pyrrolidone of varying molecular weights and available from GAF Corporation of the U.S.A. under the trade designation "PLASDONE" including Plasdone K-29/32 and Plasdone K-90. Plasdone

K-29/32 has a volume average molecular weight of approximately 38,000. K-90 has a volume average molecular weight of approximately 630,000.

SUMM In accordance with a further aspect of the present invention there is provided a method of preparing a **veterinary implant** as described above, which method includes

SUMM (b) a **veterinarily** acceptable carrier or excipient selected to provide, in combination with the active ingredient (a), in use a generally continuous release rate of active ingredient sufficient to maintain blood melatonin or its equivalent at, or above, natural night time levels;

SUMM (3) compressing the mixture under a pressure and temperature sufficient to form a **veterinary implant**.

SUMM The mixture is then subjected to a compression step. Compression may be carried out at a temperature in the range of from room temperature to approximately 90.degree. C. The temperature selected will be dependent upon the stability of the active ingredient and the **veterinarily** acceptable carrier or excipient selected. The compression may be conducted under pressures of up to several hundred bar, for example 5 to 1200 bar. Preferably compression is undertaken with pressures of approximately 1 to 800 bar. The **veterinary implant** may be compressed into any suitable form. For example, the **veterinary implant** may be in the form of a tablet, a bead, a cylinder, a rod or a plate. A tablet form is preferred. In this form, a standard tablet press may be used.

SUMM In a still further aspect of the present invention there is provided a method of preparing a **veterinary implant** which includes

SUMM (4) compressing the granulated mixture under a pressure and temperature sufficient to form a **veterinary implant**.

SUMM Where the granulation step is a wet granulation step, the **veterinarily** acceptable carrier (b) may be provided in the form of a solution. An alcohol solution may be used.

SUMM The **implants** may be individually loaded into a separate chamber of a plastic cartridge. The plastic cartridges may be placed into a "gun" and the **implant** delivered subcutaneously through a large bore needle.

SUMM It has been found that **implants** prepared utilizing the above described methods may be cheaply and efficiently manufactured and lend themselves to mass production techniques. The **implants** so formed have been found to release the active ingredient at a generally continuous rate sufficient to maintain blood melatonin or its equivalent at, or above, the natural night time levels of the subject **animal**. Thus the **veterinary implants** are suitable for use in the reproductive regulation methods according to the present invention.

SUMM Accordingly, in a further aspect of the present invention there is provided a method of modifying the seasonal breeding activity of **animals** which method includes inserting into an **animal** to be treated a **veterinary implant** including an effective amount of (a) an active ingredient selected from melatonin, related indoles and derivatives thereof, or mixtures thereof and (b) a **veterinarily** acceptable carrier or excipient selected to provide, in use, in combination with the active ingredient sufficient to maintain blood melatonin, or its equivalent, at, or above, natural night time level.

SUMM The **animal** to be treated may be a mature **animal** and the seasonal breeding activity is modified by accelerating the onset of the breeding season.

SUMM The **animal** to be treated may be a pre-pubescent **animal** and the seasonal breeding activity is modified by delaying the onset of puberty and thus the onset of the breeding season is altered over a number of years.

SUMM In general, the **animal** to be treated will be a female. Particularly significant results are achieved when the **animals** treated are maiden females. However, alternatively or in addition the male of the species may be treated. This is preferable for deer and goats, and to a lesser extent, **sheep**.

DETD **Veterinary implants** according to the present invention are prepared in utilizing the ingredients and methods of manufacture as specified below. In each example the ingredients were intimately mixed together and, where stated, wet granulated utilizing an alcohol solvent.

DETD The **implants** are manufactured from the above powders using standard tabletting techniques.

DETD The mixtures or granulated mixtures were then compressed to form a **veterinary implant** in tablet form utilizing a tablet press. Each of the **implants** function satisfactorily but superior results were achieved utilizing the wet granulation and compression method. The **implant** manufactured according to example 7 was also found to be superior as a continuous blood melatonin was maintained above 100 pg/ml for a longer period than with other **implants**. The reduced melatonin **implant** manufactured according to example 15 was found to be effective in modification of breeding activity with substantially reduced melatonin contents.

DETD

MELATONIN **IMPLANTS**

Note: All weights of Ingredients in mg

	1	2	3
Melatonin	20	20	10
P.V.P. (10%)	1	1.2	1
Beeswax	1	1	1
Dibutylphlate	0.1	--	0.1
Lubritab .RTM.	1	1	--
Zn Stearate	--	--	1
Encompress .RTM.	--	--	5

Method of Manufacture: Wet Granulation and Compression

	4	5	6
Melatonin	10	10	15
Encompress .RTM.	5	5	5
Lubritab .RTM.	1	1	0.8
Mg. Stearate	--	0.4	--

Method of Manufacture: Direct Compression

	7	8
Melatonin	20	20
P.V.P. K (5%)	0.2	0.3
Cellulose Acetate Phthalate	--	2
Lubritab .RTM.	0.3	0.3

Method of Manufacture: Wet Granulation and Compression

	9
Melatonin	20
Methocel A15C Prem	2 granulate with alcohol
Lubritab .RTM.	0.3

Method of Manufacture: Wet Granulation and Compression

	10	12
Melatonin	20	20
P.V.P. K-90 10%	qs to 0.64	qs to 1.11
(alcohol) granulate	granulate twice	
Lubritab .RTM.	0.64	0.64

Method of Manufacture: Wet Granulation and Compression

	11	13
Melatonin	20	20
Ethylcellulose 10%	qs to 0.59	qs to 1.09
(alcohol) granulate	granulate twice	
Lubritab .RTM.	0.64	0.62

Method of Manufacture: Wet Granulation and Compression

	14
Melatonin	20
P.V.P. K-90 10%	qs to 0.64
(alcohol) granulate	
Ethylcellulose 10%	qs to 0.49
(alcohol) granulate	0.64
Lubritab .RTM.	

Method of Manufacture: Wet Granulation and Compression

Implants with Reduced Melatonin Content

	15	16	17
Melatonin	12.5	5	2
granulate with PVP-K-90 Encompress .RTM.	12.9	26.1	31.5
Lubritab .RTM. 3%	0.7	1.0	1.1
implant weights	26.6	32.4	34.5

Method of Manufacture: Wet Granulation and Compression

DETD Experiments exploring the effects of continuous melatonin administration were carried out on ten Border Leceister.times.Merino ewes. The ewes were housed in an **animal** house under a lighting regime simulating the normal change in photoperiod occurring at that time of year. To provide a continuous source of melatonin subcutaneous **implants** were prepared. These **implants** were in the form of melatonin filled sachets constructed from two 25 mm square silasticmedical grade sheets (0.125 cm thick: Dow Corning, Midland, Mich. U.S.A.) with edges cemented together with silastic glue. Invitro tests showed that **implants** of this size released between 100-150 ug melatonin per day with buffered protein (1% albumin) solution; the amount needed, as calculated from production rate studies, to maintain blood melatonin continuously at nightime levels. Five ewes were **implanted** subcutaneously with melatonin filled sachets

and 5 with empty sachets as controls.

DETD Blood samples (19.times.20 min), taken 5 days before and 17 and 30 days after the subcutaneous placement of the sachets, showed that in the treated **animals** blood levels of melatonin were maintained at 100-180 pg/ml in the controls. After 17 days of treatement blood prolactin levels had decreased dramatically in the melatonin group 11.+-.ng/ml (.+-.SD) compared with 134.+-.29 ng/ml in the control group. Analysis of single daily samples indicated that this decrease had occurred as early as 7 days after **implantation**.

DETD The results in **sheep** indicated that constant melatonin administration exerted a similar effect of plasma prolactin levels to daily oral administration (Aust. Patent Application No. 78305/81) but that the effect was achieved more rapidly i.e. approx. 7 days compared to approx. 20-30 days with the oral route.

DETD This result was unexpected as according to previous experiments mainly carried out with laboratory rodents continuous melatonin administration should have had consequences similar to long day length and thus opposite to those obtained with daily administration. Similar results were achieved utilizing **veterinary implants** as preferred in examples 1 to 17.

DETD In a further experiment beeswax and melatonin were mixed at 140.degree. C. and drawn into polyethylene tubing of either 2.2 mm or 2.0 mm diameter. Various proportions of melatonin/beeswax were used e.e. 1:24, 3:22, 10:15. 4 mm lengths of the material were then **injected** intramuscularly into an ear, or subcutaneously into the face or back of a group of wethers. Blood samples were then taken weekly for 8 weeks and blood assayed for melatonin. Using this approach it was shown that beeswax **implants** (10:15 aMT:BW, total length 8 mm diameter 2.2 mm) when **injected** into an ear muscle produced stable blood levels of melatonin excess of 100 pg/ml for up to 8 weeks.

DETD Thus according to the invention it has been found that constant melatonin availability in a **sheep** (which is a short day breeding species) has consequences similar to short day length that is blood prolactin decreases. This is in contrast to results from long day breeding species like the hamster and which constant melatonin availability has consequences similar to long day length.

DETD It has also been found that melatonin can influence the age at which puberty occurs in ewe **lambs**. The age at which puberty occurs in ewe **lambs** is determined in part by the season of birth and in part by prevailing photoperiod conditions. Thus **animals** born in autumn or winter have puberty delayed until the following autumn, corresponding to the time of onset of puberty of younger **lambs**.

DETD By the use of melatonin **implants** as in examples 1 to 17, the time of the onset of puberty and the long term seasonality of the ewe can be adjusted as indicated by an experiment in which five ewe **lambs** born in April 1981 to pinealectomized ewes **implanted** s.c. with melatonin sachets and 6 ewe **lambs** **implanted** with empty sachets.

DETD Puberty (determined by weekly **progesterone** analysis) was delayed (P<0.05) in 4 of the 5 melatonin-treated ewe **lambs**; means pubertal age of ewes with empty **implants** was 44 weeks of age compared to 45, 63, 72, >72, >72 weeks of age for the melatonin-treated **animals**. The seasonal difference in the timing of the onset of breeding activity again occured during Spring in the melatonin treated **animals** as opposed to late Summer/Autumn in the ewes, with treated empty **implants**.

CLM What is claimed is:

1. A **veterinary implant** tablet comprising: (a) about 2 to 15% by weight based on the total weight of said tablet of a fatty acid salt compression binder; (b) about 25 to 50% by weight based on the total weight of said tablet of a directly compressible vehicle selected from the group consisting of calcium phosphate and derivatives thereof; (c) about 1 to 5% by weight based on the total weight of said tablet of a granulating agent; and (d) an amount of melatonin effective to maintain blood melatonin at, or above, a natural nighttime level of an

animal to be treated for a period of time effective to accelerate an onset of breeding activity in mature **animals** or to delay an onset of puberty in prepubescent **animals**; wherein said **implant** tablet provides a substantially continuous release rate of melatonin so as to maintain blood melatonin at, or above, said level for said period of time.

2. The **veterinary implant** tablet of claim 1 wherein the blood melatonin is maintained at a level at, or above, about 100 pg/ml, and the **animal** to be treated is a domesticated **ruminant**.

3. The **veterinary implant** tablet of claim 1 wherein the granulating agent is selected from the group consisting of ethyl cellulose, methyl cellulose, cellulose acetate, cellulose acetate phthalate, vinyl polymers, waxes and mixtures thereof.

4. The **veterinary implant** tablet of claim 3 wherein the granulating agent includes a polyvinyl pyrrolidone having a molecular weight selected to provide an effective release rate of melatonin.

5. A method for preparing a **veterinary implant** tablet which method comprises: (1) providing (a) about 2 to 15% by weight based on the total weight of said tablet of a fatty acid salt compression binder; (b) about 25 to 50% by weight based on the total weight of said tablet of a directly compressible vehicle selected from the group consisting of calcium phosphate and derivatives thereof; (c) about 1 to 5% by weight based on the total weight of said tablet of a granulating agent; and (d) an amount of melatonin effective to maintain blood melatonin at, or above, a natural nighttime level of an **animal** to be treated for a period of time effective to accelerate an onset of breeding activity in mature **animals** or to delay an onset of puberty in prepubescent **animals**; (2) mixing the components of step 1; and (3) compressing the mixture under a temperature and pressure sufficient to form the **veterinary implant** tablet; wherein said tablet provides a substantially continuous release rate of melatonin so as to maintain blood melatonin at, or above, said level for said period of time.

6. A method of modifying the seasonal breeding activity of **animals**, which comprises administering to an **animal** to be treated a **veterinary implant** tablet comprising: (a) about 2 to 15% by weight based on the total weight of said tablet of a fatty acid salt compression binder; (b) about 25 to 50% by weight based on the total weight of said tablet of a directly compressible vehicle selected from the group consisting of calcium phosphate and derivatives thereof; (c) about 1 to 5% by weight based on the total weight of said tablet of a granulating agent; and (d) an amount of melatonin effective to maintain blood melatonin at, or above, a natural nighttime level of an **animal** to be treated for a period of time effective to accelerate an onset of breeding activity in mature **animals** or to delay an onset of puberty in prepubescent **animals**; wherein said **implant** tablet provides a substantially continuous release rate of melatonin so as to maintain blood melatonin at, or above, said level for said period of time.

7. The method of claim 6 wherein the blood melatonin is maintained at, or above, a level of about 100 pg/ml, and the **animal** to be treated is a domesticated **ruminant**.

8. The method of claim 7 wherein the **animal** is a mature **animal** and the seasonal breeding activity is modified by accelerating the onset of the breeding season.

9. The method of claim 5 wherein the **animal** is a pre-pubescent

animal and the seasonal breeding activity is modified by delaying the onset of puberty.

IT Goat
IT **Ruminant**
IT **Sheep**
(reprodn. regulation in, with melatonin-contg. implant)
IT 9003-39-8 9004-35-7 9004-38-0 **9004-57-3 9004-67-5**
10103-46-5
(implant contg. melatonin and, for reprodn. regulation in ruminants)